VOLUME 81 • FEBRUARY 1959 • NUMBER 2

A.M.A. ARCHIVES OF NEUROLOGY & PSYCHIATRY

SECTION ON NEUROLOGY

Acetylcholine in the Mechanism of Headaches of Migraine Type

R. Charles Kunkle

Electrocardiographic Alterations Observed During Percutaneous Cerebral Angiography

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Course of a Neurotropic Toxin to the Central Nervous System

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Raymond D. Adams, Maurice Victor, and Elliott L. Mancall

Interaction in Simultaneous Motor Functions

Prof. Dr. Irena Housmanowa-Petrusewicz

Extraocular Motor Disturbances in Primary Brain Tumors

Thomas C. Parsons

Abstracts from Current Literature

News and Comment

Books

SECTION ON PSYCHIATRY

Personality Growth in Psychiatric Residents

Robert R. Holt

Water-Loading Test in Mental Diseases

J. D. Stevens, F. A. Majka, and F. L. Humoller

Effect of Two Psychological Stresses on Adrenocortical Function

Harold Persky, Sheldon J. Korchin, Harold Basowitz, Francis A. Board, Melvin Sabshin, David A. Hamburg, and Roy R. Grinker

Role of Anxiety in Psychophysiologic Reactions

Judith Franks, George M. Haslerud, G. Donald Niswander, and Thomas M. Casey

Periodic Phenomena and the Thyroid

Curt P. Richter, Georgeanna S. Jones, and Lorraine Biswanger

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TABLE OF CONTENTS

VOLUME 81 FEBRUARY 1959 NUMBER 2

SECTION ON NEUROLOGY

ORIGINAL ARTICLES

PAGE

Acetylcholine in the Mechanism of Headaches of Migraine Type
R. Charles Kunkle, M.D., Durham, N. C. 135

Electrocardiographic Alterations Observed During Percutaneous Cerebral Angiography
Joseph A. Epstein, M.D.; Irwin Hoffman, M.D., and Bernard S. Epstein, M.D., New Hyde Park, N. Y. 142

Course of a Neurotropic Toxin to the Central Nervous System
Alexander A. Fedinec, M.A., and Howard A. Matzke, Ph.D., Lawrence, Kan. 148

Central Pontine Myelinolysis
Raymond D. Adams, M.D.; Maurice Victor, M.D., and Elliott L. Mancall, M.D., Boston 154

Interaction in Simultaneous Motor Functions
Prof. Dr. Irena Housmanowa-Petruscewicz, Warsaw, Poland 173

Extraocular Motor Disturbances in Primary Brain Tumors
Thomas C. Parsons, M.M.Sc., M.D., Montrose, N. Y. 182

REGULAR DEPARTMENTS

Abstracts from Current Literature 189
News and Comment 200
Books 201

SECTION ON PSYCHIATRY

ORIGINAL ARTICLES

Personality Growth in Psychiatric Residents
Robert R. Holt, Ph.D., New York 203

Water-Loading Test in Mental Diseases
J. D. Stevens, M.D.; F. A. Majka, M.D., and F. L. Humoller, Ph.D., Sepulveda, Calif. 216

Effect of Two Psychological Stresses on Adrenocortical Function
Harold Persky, Ph.D.; Sheldon J. Korchin, Ph.D.; Harold Basowitz, Ph.D.; Francis A. Board, M.D.; Melvin Sabshin, M.D.; David A. Hamburg, M.D., and Roy R. Grinker, M.D., Chicago 219

Role of Anxiety in Psychophysiologic Reactions
Judith Franks, M.A.; George M. Haslerud, Ph.D.; G. Donald Nisewander, M.D., and Thomas M. Casey, M.A., Concord, N. H. 227

Periodic Phenomena and the Thyroid
Curt P. Richter, Ph.D.; Georgeanna S. Jones, M.D., and Lorraine Bisexamger, M.D., Baltimore 233

Studies with a New Hallucinogen
Adrian M. Ostfeld, M.D.; Harold Visotsky, M.D.; Leo Abood, Ph.D., and Binyamin Z. Lebovitz, Ph.D., Chicago 256

REGULAR DEPARTMENTS

Books 264

A. M. A.
Archives of Neurology and Psychiatry

VOLUME 81 FEBRUARY 1959 NUMBER 2

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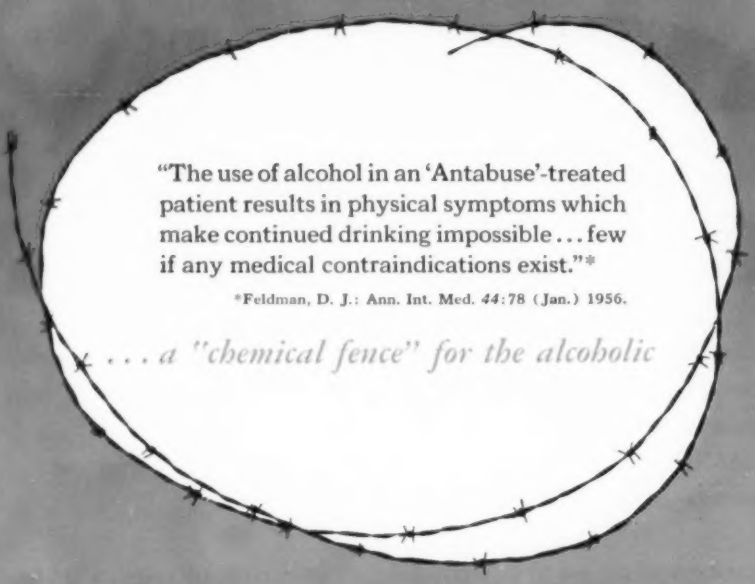
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CHARACTER DISORDERS	15	13
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TOTALS	145	105

by symptom

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SECTION ON
NEUROLOGY

Acetylcholine in the Mechanism of Headaches of Migraine Type

E. CHARLES KUNKLE, M.D., Durham, N. C.

In spite of the many clues which point to dilatation of extracranial or intracranial arteries as essential in the mechanism of migraine headache, the immediate cause of the vasodilatation has not yet been defined.[1] This report examines the hypothesis that acetylcholine may be the chemical agent responsible for the relaxation of the arterial wall.

Incentives to search for acetylcholine are certain accessory symptoms and signs which accompany migraine headache in some patients. These clues, often so trivial as to be overlooked, suggest a centrally integrated neural discharge over parasympathetic pathways. Commonest are nasal congestion and excessive lacrimation, probably resulting from impulses over the greater superficial petrosal branch of the facial nerve. Rare, but no less significant, are miosis, more marked on the side of the pain when the headache is unilateral, and bradycardia, presumably mediated by the oculomotor and vagus nerves, respectively. An alternative interpretation, that many of these features represent unilateral sympathetic "hypofunction," has also been suggested, particularly by Jacobsen.[2] Experimental support for this view is lacking.

Submitted for publication April 3, 1958.

From the Division of Neurology, Duke University Medical Center.

Read before the 83d Annual Meeting of the American Neurological Association, Atlantic City, June 17, 1958.

The route of vasodilator nerves to superficial head vessels is unknown. That to intracranial arteries is not fully charted but, on the basis of recorded anatomic and physiologic studies in lower mammalian forms, may be via small branches of the facial nerve to the sheath of the internal carotid artery just as it enters the middle fossa.[3] Observations by Forbes and Cobb, moreover, indirectly implicate acetylcholine in the activity of this pathway. Their ingenious experiments revealed that in the monkey, at least, the dilatation of pial arteries evoked by stimulation of the facial nerve at the geniculate ganglion can be blocked by preliminary application of atropine 0.5% to these arteries.[4]

If acetylcholine is released in the walls of certain cranial arteries in the migraine attack, a portion may enter the blood stream. Here it is undoubtedly soon destroyed by the ample supply of circulating cholinesterases. The chances are slight, therefore, that it could be detected, even early in the headache. Explorations in this direction have been reported by Torda and Wolff[5] and by Jiménez Díaz and co-workers.[6] Using bioassay methods applied to urine samples from patients with migraine headaches, both laboratories uncovered a substance of unknown nature. In its effects upon various test tissues, it somewhat resembled, but was clearly not identical with, acetylcholine.

Another and more direct approach to this biochemical problem is one aimed at the vicinity of the dilated arteries. Facial and scalp vessels are accessible, but an attempt to demonstrate a discharge of acetylcholine into these tissues would present formidable technical difficulties. The *intracranial* arteries, however, are bathed in cerebrospinal fluid, a sample of which can readily be obtained by lumbar puncture. In addition is the advantage that in man this fluid normally contains no detectable acetylcholine and exhibits very little cholinesterase activity. Early studies by Nochimowski, relying upon leech muscle for bioassays, suggested the presence of acetylcholine in cerebrospinal fluid in a wide variety of neurologic and psychiatric disorders.[7] These observations have not been confirmed, even by more sensitive techniques employing the mollusc heart, except for the detection of minute amounts of an acetylcholine-like substance in some patients with epileptic disorders or severe cerebral trauma.[8,10]

Accordingly, the present study was focused upon patients in whom the headache of migraine type appeared to arise in part at least from *intracranial* arteries. This kind of headache is identified by the following characteristics: distinct accentuation anteriorly on mild or moderate rotary head jolt, absence of change during manual compression of scalp arteries, mild improvement during the latter portion of a 10-second period of straining (the Valsalva maneuver), and, of particular diagnostic value, sharp accentuation beginning one to two seconds after release of the strain and lasting for several seconds. Also of aid in separating intracranial from extracranial vascular pain is the resistance of intracranial headache to a therapeutic trial of parenterally administered ergotamine tartrate. In some patients the responses to these maneuvers may suggest that both intra- and extracranial arteries are at fault. Occasionally, the reports made by the patient are inconclusive, but in most instances a tenable anatomic inference can be made.[11]

For this projected study "cluster" headache (otherwise known as "histaminic cephalalgia") was of particular value. This migraine variant, high in intensity and relatively brief in duration, usually presents in bouts of headache occurring in rapid succession, once or more each 24 hours. Once a series of headaches has begun, the patient is uniquely accessible to study.[12] Furthermore, the pain is in some patients intracranial and in others extracranial, and the accessory features of parasympathetic overflow listed above are found more frequently than in other types of migraine. For these reasons, the disorder is especially appropriate for physiologic analysis.

It is to be noted that the project here reported arises from a chain of hypotheses: (1) that some forms of migraine headache are attributable to painful dilatation of intracranial arteries; (2) that the vasodilatation is neurogenic and employs, as the end-organ mediator, acetylcholine, and (3) that acetylcholine, thus released in intracranial arterial walls, may diffuse sufficiently through the surrounding cerebrospinal fluid to be detected in the lumbar sac. The outcome of the search for acetylcholine hinges upon the validity of these assumptions, some of which clearly remain open to question and modifications.

Methods

Adult patients with various neurologic illnesses were selected for study from the inpatient services at Duke Hospital and the adjacent Veterans Administration Hospital. Technically satisfactory spinal-fluid assays for acetylcholine were possible in 74 patients, of whom 37 had headaches of several different types. The remaining 37 served as general controls. They had assorted illnesses, including degenerative, vascular, inflammatory, or neoplastic diseases of the nervous system; 8 had epileptic disorders; none had recent head injury.

The 37 patients with headache were the group of prime interest, especially the 22 with recurrent headache of migraine type, including 14 cases of "cluster" headache. The classification of these patients according to manifest or suspected headache mechanisms is indicated in Table 1. In all but 2 of the 37 patients headache was present at the time of lumbar puncture for removal of a cerebrospinal-fluid sample; the headache had

TABLE 1.—*Cerebrospinal Fluid Assays in Thirty-Seven Patients with Headache*

Headache Mechanism		Assay Results	
		Acetylcholine-like Reaction	No Acetylcholine-like Reaction
Vascular (migraine type)	22 *		
Intracranial (8)		4	4
Extracranial (10)		0	10
Mixed (1)		1	0
Uncertain (3)		0	3
Muscle-contraction type	10	0	10
Conversion reaction	2	0	2
Trigeminal neuralgia	1	0	1
Undetermined	2	0	2
	37	5	32

* Of the 22 patients with vascular headache, 14 were male. The five assays demonstrating an acetylcholine-like reaction were in the male group.

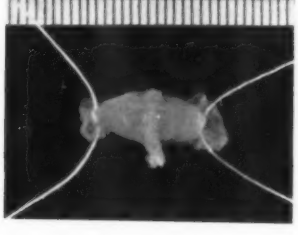
usually begun several hours before. Of the 37, 21 were female.

Assays for acetylcholine were carried out by the biologic method described by Tower and McEachern.[13,14] More sensitive than any chemical procedure yet developed and highly specific for acetylcholine, it employs the heart of Venus mercenaria, the common hard-shell clam (Fig. 1), immersed in a 20 ml. sea-water chamber and attached to a light lever recording on a drum kymograph. To each 5 ml. sample of cerebrospinal fluid at the time of collection were added 1.0 ml. of 0.1 N HCl, 2.0 ml. of 0.9% NaCl, and 1.0 ml. of neostigmine methylsulfate 1:4,000. This mixture, maintained under refrigeration at 5 C, has been shown by Tower to preserve acetylcholine well for a week or more.[13] Bloody samples, unsatisfactory for analysis because of the large amounts of cholinesterases which may be carried into the specimen, were rejected. The assays were completed within 7 days of collection, a large majority within 48 hours. One step in the technique used by Tower, the addition to the sample of a small volume of NaOH solution to restore a pH close to neutral immediately prior to assay, was omitted in these experiments. This modification was made to minimize hydrolysis of acetylcholine in specimens to be held for extended study if the initial test should yield a positive result. Assays were restricted to fall, winter, and early spring seasons to avoid the decline in sensitivity of the Venus heart which is evident in summer months. When necessary, a sluggish heart was made to beat more forcefully for the assays by the addition to the chamber of ergonovine maleate U. S. P. 0.02 mg., a technique of tested value.[13]

The biologic response indicating an acetylcholine-like substance was a progressive weakening of the heart beat, beginning a few contractions after addition of the test sample. This reaction, here defined as presumptively positive, was checked by retest and compared with graded responses to known amounts of acetylcholine in the conventional bioassay method. Moderate variation in sensitivity of the test tissue was evident from week to week. No clam heart was used unless it responded to concentrations of acetylcholine in the chamber at least as low as 0.001μg/ml. of sea water. With correction for dilution factors involved in the collection of the lumbar puncture specimens and the use of 2 ml. samples in the test chamber, a heart of this sensitivity could detect 0.02μg. of acetylcholine per milliliter of cerebrospinal fluid. In many experiments the heart was even more sensitive, detecting as little as 0.001μg/ml. of cerebrospinal fluid.

Confirmatory Tests.—When benzoquinonium (Mytolon) chloride,* which effectively blocks acetylcholine depression of the clam heart,[15] became available after the initial phase of this study, it was used routinely to confirm acetylcholine-like reactions. This agent was added to the test chamber in a 50μg. amount and allowed to remain in contact with the heart for 3 to 12 minutes before the specimen was retested. Additional evidence for the presence of acetylcholine in cerebrospinal fluid giving a positive reaction was sought by retest after hydrolysis of a portion of the specimen, provided a sufficient volume remained. This procedure (alkalization, heating, and then neutralization) destroys whatever acetylcholine may be present.[16] A third method of confirmation, introduced late in the study, employs a duplicate sample of cerebrospinal fluid from which neostigmine has been withheld and which is unrefrigerated. If the basic sample, collected and prepared by the usual methods, gives a positive bioassay reaction which

Fig. 1.—Isolated heart of Venus mercenaria. Ligatures are placed at the auriculoventricular junctions. The two auricles are partly trimmed.



Kunkle

* Mytolon chloride (WIN 2747) was supplied for these experiments through the courtesy of Dr. M. L. Tainter, Sterling-Winthrop Research Institute, Rensselaer, N. Y.

is due to acetylcholine or a related substance, the unprotected sample should be negative.

Results

In the group of 37 patients with diseases other than headache, no acetylcholine was found in the cerebrospinal fluid samples except for those from 2 patients with grand mal seizures. In one patient the most recent convulsion was 25 hours before lumbar puncture, in the other, 10 days; acetylcholine-like effects equivalent, respectively, to 0.004μg. and 0.005μg. per milliliter of cerebrospinal fluid were recorded.

In none of the patients with headaches diagnosed as nonvascular was an acetylcholine-like reaction found (Table 1). Among the 22 with headache diagnosed as vascular, however, the assays demonstrated an acetylcholine-like substance in 5, all male. In amount, it was equivalent to 0.004μg.-0.06μg. of acetylcholine per milliliter of cerebrospinal fluid. In four of these patients the headache appeared to be intracranial in origin, and in one, both intracranial and extracranial. In each case, headache was present at the time of lumbar puncture—in three for 10-48 hours and in two for 15-30 minutes.† Additional data with reference to the five assays indicating the presence of an acetylcholine-like substance, including methods of confirmation used, are summarized in Table 2. Representative samples of the kymograph records of two assays are shown in Figure 2.

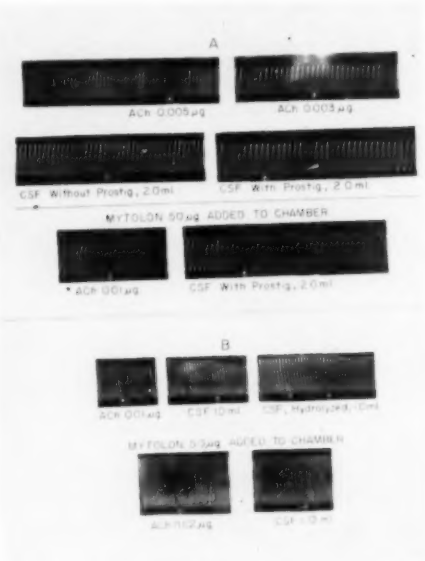


Fig. 2.—Acetylcholine-like effects upon the Venus heart of cerebrospinal fluid from patients with vascular headaches.

A (Case 4), "cluster" headache of mixed type; confirmation of acetylcholine nature of the effect by comparison with that of an additional CSF sample without the protection of neostigmine, and also by benzoquinonium (Mytolon) blockade.

B (Case 5), a migraine variant of intracranial type; confirmation by comparison of the effect with that of a hydrolyzed CSF sample, and also by benzoquinonium (Mytolon) blockade.

In four cases (instances of multiple sclerosis, cerebral thrombosis, probably degenerative encephalopathy, and muscle-contraction headache) the assays yielded an anomalous result. After addition of the cerebrospinal fluid sample to the test chamber, the heart continued to contract normally for four to seven systoles and then abruptly halted in diastole. In three cases assays were repeated with hydrolyzed samples; in two of these the reaction persisted despite the hydrolysis. The mechanism of this reaction, clearly different from the graded depression characteristic of acetyl-

† Brief case histories of the patients with "positive" assays are presented in the "Appendix."

TABLE 2.—*Patients with Headache and Acetylcholine-like Cerebrospinal Fluid Reactions*

Case No.	Diagnosis	Duration of Headache *	Acetylcholine-like Substance, μg. per Ml. CSF	Type of Confirmation of Assay
1	"Cluster" headache, variant, intracranial	10 hr.	0.06	—
2	"Cluster" headache, variant, intracranial	18 hr.	0.01	Repetition of assay on same sample 3 days later
3	"Cluster" headache, intracranial	15 min.	0.05	Mytolon blockade
4	"Cluster" headache, mixed type	30 min.	0.004	Mytolon blockade; withholding of neostigmine
5	Atypical migraine, intracranial	48 hr.	0.02	Mytolon blockade; hydrolysis

* At time of removal of cerebrospinal fluid specimen by lumbar puncture.

choline, remains undetermined. It may represent a hidden artifact or an unidentified novel substance in the cerebrospinal fluid of these few patients. None of the assays revealed a definite stimulation of the heart, such as might have resulted from the presence of serotonin.[10]

Comment

These results lend considerable support to the basic hypothesis that acetylcholine participates in the mechanism of migraine headache. The presumptively positive assays, confirmed by different methods, point strongly to the release of acetylcholine or a similar substance into the cerebrospinal fluid during headache due to dilatation of intracranial arteries. Yet many questions remain unanswered. No bioassay method can identify an unknown with absolute certainty, and present chemical methods for the detection of acetylcholine are still not sufficiently sensitive to be confirmatory.[17]

The negative assays in one-half of the patients with intracranial vascular headaches require further consideration. Possible explanations include release of the vasodilator substance in amounts too small to be detected, unduly rapid breakdown of the substance at the site of its action, limited diffusion across vessel walls and through the subarachnoid spaces, or the concomitant presence in some cerebrospinal fluid specimens of agents, such as serotonin, with opposing effects upon the clam heart.[10,18] The most favorable circumstances for finding acetylcholine in studies of this type, if this agent is released as postulated, are still uncertain; a much larger series of experiments would be required to define the many variables. Finally, there remains the possibility which Dale has emphasized, that the chemical agent of the peripheral parasympathetic system need not always be acetylcholine, even though no certain clues to an alternative substance are yet available.[19]

If acetylcholine actually is an essential link in the recurrent headaches of migraine and its variants, efforts are warranted to block its action. Little evidence is yet on record concerning specific studies of the action of atropine or similar drugs in patients with migraine. It is probable that if any of these agents can be of aid, it should best be administered in the earliest moments of the attack or in a daily prophylactic schedule. Failure of atropine to prevent or modify the headache might be anticipated, even though acetylcholine is at fault, if, as Dale has suggested, the atropine is unable to reach the immediate site of acetylcholine action in sufficient concentration to raise an effective blockade.[19,20] It seems possible, also, that central actions of atropine, about which little is known, may sometimes be excitatory to the parasympathetic outflow, opposing the peripheral action. Answers can come only from systematic and adequately controlled trials of the atropine group in patients with various forms of migraine-type headache.

Summary and Conclusions

By use of a sensitive and specific bioassay method, an acetylcholine-like substance was detected in the cerebrospinal fluid of five of nine patients during headache of the migraine type presumed to arise from dilatation of intracranial arteries.

No such substance was found in specimens from a group of 28 patients with extracranial vascular headache or headache due to nonvascular or uncertain mechanisms; none was detected in specimens from patients with miscellaneous other neurologic disorders, except for two patients with epileptic illnesses, confirming earlier reports.

The results are consistent with, but do not prove, the hypothesis that acetylcholine or a closely allied substance is an active participant in the mechanism of headaches of the migraine type.

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REFERENCES

1. Wolff, H. G.: Headache and Other Head Pain, New York, Oxford University Press, 1948.

2. Jacobsen, H. H.: Unilateral Sympathetic Hypofunction in Migraine, Acta psychiat. et neurol. scandinav. 27:67, 1952.

3. Chorobski, J., and Penfield, W.: Cerebral Vasodilator Nerves and Their Pathways from the Medulla Oblongata, Arch. Neurol. & Psychiat. 28:1257, 1932.

4. Forbes, H. S., and Cobb, S. S.: Vasomotor Control of Cerebral Vessels, Brain 61:221, 1938.

5. Torda, C., and Wolff, H. G.: Experimental Studies on Headache: Pharmacodynamics of Urine Excreted During Migraine Headache and Its Relation to 17-Ketosteroid Content, J. Clin. Invest. 22:853, 1943.

6. Jiménez Díaz, C.; Lorente, L.; Marcos, M., and Ortega, A.: Observations on the Nature and Physiopathology of Migraine, Bull. Inst. M. Res. Madrid 8:35, 1955.

7. Nochimowski, C.: Sur la présence dans le fouide céphalo-rachidien d'une substance du type de l'acétylcholine, au cours de certaines affections d'ordre neurologique ou psychiatrique, J. physiol. et path. gén. 35:746, 1937.

8. Tower, D. B., and McEachern, D.: Acetylcholine and Neuronal Activity: I. Cholinesterase Patterns and Acetylcholine in the Cerebrospinal Fluid of Patients with Craniocerebral Trauma, Canad. J. Res., Sect. E. 27:105, 1949.

9. Tower, D. B., and McEachern, D.: Acetylcholine and Neuronal Activity: II. Acetylcholine and Cholinesterase Activity in the Cerebrospinal Fluid of Patients with Epilepsy, Sect. E. 27:120, 1949.

10. Reference deleted.

11. Sachs, E., Jr.: Acetylcholine and Serotonin in the Spinal Fluid, J. Neurosurg. 14:22, 1957.

12. Kunkle, E. C., and Wolff, H. G.: Headache, in Clinical Neurology, edited by A. B. Baker, New York, Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 1955.

13. Kunkle, E. C.; Pfeiffer, J. B., Jr.; Wilhoit, W. M., and Hamrick, L. W., Jr.: Recurrent Brief Headache in "Cluster" Pattern, Tr. Am. Neurol. A. 77:240, 1952.

14. Tower, D. B., and McEachern, D.: Experiences with the "Venus" Heart Method for Determining Acetylcholine, Canad. J. Res., Sect. E. 26:183, 1948.

15. Tower, D. B.: Preservation of Acetylcholine in Human Cerebrospinal Fluid: A Simple Method for Clinical Use, Canad. J. Res., Sect. E. 27:20, 1949.

16. Ludueña, F. P., and Brown, T. G., Jr.: Mytolon and Related Compounds as Antagonists of Acetylcholine on the Heart of Venus Mercenaria, J. Pharmacol. & Exper. Therap. 105:232, 1952.

17. MacIntosh, F. C., and Perry, W. L. M.: Biological Estimation of Acetylcholine, Methods M. Res. 3:78, 1950.

18. MacDonald, R. P.; Gerber, C., and Nielsen, A.: Ultramicro Determination of Acetylcholine in Cerebrospinal Fluid, Am. J. Clin. Path. 25:1367, 1955.

19. Twarog, B. M., and Page, I. H.: Serotonin Content of Some Mammalian Tissues and Urine and a Method for Its Determination, Am. J. Physiol. 175:157, 1953.

20. Dale, H. H.: Junctional Transmission of Nervous Effects by Chemical Agents, Proc. Staff Meet. Mayo Clin. 30:5, 1955.

21. Dale, H. H.: Progress in Autopharmacology, Bull. Johns Hopkins Hosp. 53:297, 1933.

APPENDIX

Brief clinical histories of patients with headache and cerebrospinal fluid assays demonstrating an acetylcholine-like effect follow.

CASE 1.—Age 42. Diagnosis: "cluster" headache, variant, intracranial in type. This metal worker was hospitalized Nov. 2, 1955, because of usually brief "cluster" headache of three weeks' duration. The attacks centered about the right orbit and occurred up to two to three times each 24 hours, mainly during the night, in very intense form, without injection of the eye or face. His past history included various other forms of headache, usually bifrontal, since the age of 15. He had stopped heavy drinking about 16 months before and for a year had been tense, tired, and depressed, feeling trapped in his stressful job. He was recently concerned by doubts that he could afford to keep his son in college. During the two weeks before admission the patient had been tried on ergotamine with caffeine (Cafergot), 2 tablets at bedtime, repeated in three hours, but these failed to block any of the nocturnal headaches.

He was admitted with intense headache of 10 hours' duration, beginning while he was en route to the hospital. It was made worse on rotary jolt or strain. Atropine 1.0 mg., administered intravenously shortly after admission, was without benefit, and ergotamine tartrate 0.5 mg., then given intravenously, after lumbar puncture, was of uncertain value. Atropine, given again intravenously the next morning, 15 minutes after the onset of another headache, was followed by disappearance of the pain within 12 minutes. Later that day he was given saline intravenously at the 40th minute of another attack and ergotamine intravenously 10 minutes later, both without benefit. Atropine was then given at the 60th minute, with slight

reduction in headache within 15 minutes. On the third hospital day ergotamine was tried for two separate headaches, without benefit, but atropine, 30 minutes after the onset of one attack, was followed by clearing of the headache within 1 minute but moderate return 17 minutes later. Observation of the headaches indicated that they were increased transiently by rotary head jolt or one-second strain, or for 10 seconds after a 10-second strain.

CASE 2.—Age 32. Diagnosis: "cluster" headache, variant, intracranial in type. This married farmer was seen first as an outpatient on Nov. 7, 1955, with bifrontotemporal throbbing headaches with nausea and vomiting, occurring sometimes daily or, again, only every few months since childhood. One month before his visit he began to have brief, but intense, nocturnal headaches, centered in the right fronto-orbitotemporal area, with lacrimation and reddening of the right eye and nasal obstruction, recurring several times a day. After two weeks these attacks became less severe but almost constant, with periodic exacerbations. The pain was worse when he was lying down. He reported having had mounting tension for the past several months and several sources of repressed resentment.

He was admitted to the hospital for study two weeks later with an exacerbation of headache of 16 hours' duration, accompanied by nausea and vomiting. On admission his headache was observed to be increased by jolt or strain and to be unaffected by temporal-artery compression on the affected side. Ergotamine tartrate 0.5 mg., intravenously, was without effect, as also was atropine 1.2 mg., intravenously. A lumbar puncture was done two hours after admission. Improvement was gradual after the first hospital day on rest and light sedation.

CASE 3.—Age 34. Diagnosis: "cluster" headache, intracranial in type. This 34-year-old salesman presented a history of intense right frontal headache in three bouts in the past year, each lasting a week and consisting of as many as five headaches, about 45 minutes in duration, in 24 hours, mainly at night. With each attack he noted scleral injection and increased lacrimation on the affected side. He believed the pain was commonly worse on head jolt. Since his youth he had noted bifrontal headache on missing a meal. He had for many years been a periodic heavy drinker, a recurrent source of marital stress. Thirteen months before his visit his job as salesman was changed to one involving much traveling and pressure to meet his work schedules.

His first attack witnessed after hospitalization, on Feb. 21, 1956, was accompanied by marked reddening of the right sclera, slight drooping and swelling of the right upper lid, and a congested nose. The headache was unaltered by 10-second straining. Atropine 1.0 mg. was given intravenously at the eighth minute; the pain had almost ceased five minutes later. Lumbar puncture was done 15 minutes after the attack had begun.

During the next attack, 12 hours later, the pain was readily augmented by rotary jolt. Ergotamine tartrate 0.5 mg., given intravenously at 22 minutes, was followed by clearing of the headache within three to four minutes. For another attack, two days later, intravenous saline was of no benefit. The attacks gradually diminished in frequency before discharge and soon ceased, with no recurrences in follow-up a year later.

CASE 4.—Age 45. Diagnosis: "cluster" headache, mixed type. For four years this patient had had severe brief right or left anterior headache in clusters, one in 1952, two in 1954, and the present cluster beginning in mid-September, 1956. Each bout lasted several weeks. In the most recent cluster, of six weeks' duration, the headaches occurred daily. He believed the pain was worse on rotary jolt and unaltered by straining. The right sclera was injected during headaches on this side.

A headache began shortly after admission to the hospital, on Oct. 25. Lumbar puncture was carried out 30 minutes later. Atropine 1.2 mg. was given intravenously at the 45th minute, with no effect. Ergotamine tartrate 0.5 mg., intramuscularly 15 minutes later, was quickly followed by subsidence of pain. Two days later atropine 1.2 mg., given intravenously shortly after the onset of another attack, was followed by complete relief within a few minutes, although mild headache returned an hour later. Ergotamine tartrate 0.5 mg., given intramuscularly for a subsequent attack, was followed by quick relief.

His headaches gradually became less frequent in the ensuing three weeks and then entered a remission.

CASE 5.—Age 52. Diagnosis: atypical migraine, intracranial in type. This patient was hospitalized on Jan. 4, 1957, with almost daily bifrontotemporal headache for the preceding five months, usually beginning one-half hour after arising in the morning and becoming worse on head jolt. By temperament he was tense and driving. He had been working under pressure and reliance on alcohol for relaxation until a year before his admission.

The headache present on admission was easily made worse by rotary head jolt and its severity decreased by bilateral jugular compression. It was questionably eased during 10-second straining. Lumbar puncture was done on the 3d hospital day, after approximately 48 hours of continuous headache.

Electrocardiographic Alterations Observed During Percutaneous Cerebral Angiography

Iodopyracet (Diodrast) and Diatrizoate (Hypaque)

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The adverse effects on brain tissue of contrast media used for cerebral angiography have been reported in considerable detail. However, the physiological alterations which may occur require further investigation for a better understanding of possible complications. In this preliminary report the cardiovascular effects of iodopyracet (Diodrast) and of diatrizoate (Hypaque) are discussed.

Intracarotid iodopyracet injections produce mainly a vascular necrobiotic change affecting particularly the arterioles, followed by ischemic necrosis of surrounding parenchyma.[1] Alteration of the blood-brain barrier was demonstrated experimentally in rabbits by Broman and Olsson[2] by the passage of trypan blue into the brain parenchyma from the cerebral circulation. They postulated a chemotoxic effect on vascular endothelium, producing vasospasm, with resulting edema, vascular engorgement, and punctate hemorrhages in the central portions of the damaged areas. The intensity of injury varied with the time the contrast medium remained in contact with the involved tissues. Bassett, Rogers, and Cherry[3] demonstrated that the acidity and osmotic pressure of the medium did not appreciably influence the permeability of the blood-brain barrier.

The vasospastic effect was regarded as protective by Foltz, Thomas, and Ward,[4] who demonstrated a longer-lasting vasodilatation following the initial vasoconstriction. Stellate block and the use of warmed iodopyracet both minimize the protective vasospasm, permitting greater concentrations of iodopyracet to reach the brain tissue, where its direct cytotoxic action has been demonstrated.

Foltz, Thomas, and Ward[4] described electrocardiographic abnormalities in both humans and monkeys during and following intracarotid injection of iodopyracet. They identified a slowing of the heart rate for one to two beats, occasionally enduring as long as two minutes. Loss of the P-wave was observed. Ectopic beats occurred in one monkey for over a minute. It was considered that these alterations were the result of central nervous system changes mediated by the vagosympathetic system, and that they were not produced by a direct myocardial action or by carotid sinus stimulation. No electrocardiographic effect was observed when the injection had been made below the carotid bifurcation. Injections made through a threaded catheter reaching the base of the skull resulted in some change in pulse rate or electrocardiographic variation. This was attributed to a higher concentration of iodopyracet reaching the brain, the effects being roughly proportional to the concentration of the medium.

Browne and Stern[5] observed marked depression of blood pressure after repeated intracarotid injections of iodopyracet in cats and attributed this to direct vasodilatation of peripheral vassels. Immediate elevation, followed by a fall of blood pressure, was reported by Gordon, Brahms, Megibow,

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and Sussman [6] after intravenous injection of iodopyracet in dogs. Chemical ganglion-blocking agents could not alter this response. No significant variations in electrocardiographic patterns were found, but the pulse rate was lowered. This was believed to be due to a direct depressant action on heart muscle.

Brown [7] and Verbrugghen [8] emphasized the protective influence of general anesthesia during cerebral angiography. Sedzimer [9] considered this to be responsible for the low mortality and morbidity in his 273 angiographic studies. The reduction of painful psychologic stimuli are believed to alleviate vasospasm, although no specific evidence for this has been presented. Diminishing the concentration of iodopyracet from 35% to 25% also was credited by Sutherland, Kite, Roach, and Campbell [10] with reducing complications. Segelov [11] attributed a lower incidence of complications to the use of small quantities of iodopyracet or diatrizoate, with careful premedication and anesthesia.

Only one case of cardiac arrest in man has been reported after the injection of 20 cc. of 50% sodium iodomethamate U. S. P. (Neo-Iopax) for intravenous urography.[12] Wickbom [13] reported cardiac arrest for seven seconds after direct intra-aortic injection of 30 cc. of 70% iodopyracet, with subsequent death of the patient.

Horger, Dotter, and Steinberg [14] investigated the electrocardiographic changes incident to angiocardiography with 70% iodopyracet or 75% sodium iodomethamate. The tracings revealed tachycardia in many of the 16 patients studied. Some presented auricular or ventricular premature contractions or both. The most striking effect was a transient alteration in the T-waves and R-T segments, regarded as compatible with myocardial anoxia produced by entrance of the contrast substance into the coronary arteries. It was proposed that this might be a factor in those few cases in which death followed angiocardiography, particularly when myocardial damage was present.

Methods

Thirty-five patients examined with percutaneous cerebral angiography were utilized. These were unselected and included mainly patients suspected of brain tumors or intracranial bleeding. All were between 26 and 65 years of age, except for one 9- and one 16-year-old patient. The contrast media used were diatrizoate (Hypaque) sodium, 50% solution, and 35% and 40% solutions of iodopyracet (Diodrast). Alternate injections of 7 ml. were made. The electrocardiographic responses to each medium in the same patient were evaluated by a continuous recording of Lead II before, during, and after the injection.

The first 10 patients received general anesthesia after intubation. Five others were intubated while awake and given intravenous analgesia. The remaining patients had premedication with 100 mg. of secobarbital (Seconal) sodium and 50 mg. of promethazine (Phenergan) hydrochloride two hours preoperatively, and received 0.4 mg. of scopolamine bromide and 75 to 100 mg. of meperidine (Demerol) hydrochloride one hour later. This, together with procaine skin infiltration, was found to be so satisfactory that general anesthesia was reserved for unmanageable patients only. Twenty control injections of isotonic saline were made, with electrocardiographic tracings for comparison with those obtained during the injection of the contrast media. The effect of infiltrating the carotid sinus with 10 ml. of 1% procaine hydrochloride to determine the effect of blocking this area on subsequent angiograms was investigated in six patients, utilizing both contrast media, as well as saline controls.

Results

Eighty injections were made in 20 male and 15 female patients. Of these, 50 were on the right side and 30 on the left. The site of injections, age, type of anesthesia, and underlying pathologic condition did not influence the electrocardiographic responses. Extracarotid extravasation caused no visible effect. Thirty injections of 50% diatrizoate sodium solution, 34 injections of 40% iodopyracet, and 16 injections of 35% iodopyracet were made. There was no difference in the responses to the two concentrations of iodopyracet. No electrocardiographic alterations followed the injections of isotonic saline. Twenty patients received injections of both diatrizoate and iodopyracet for comparative evaluations.

Effects on the Electrocardiogram of Diatrizoate and Iodopyracet Injections

	Diatrizoate, (Hypaque), 50% 30 Injections			Iodopyracet, (Diodrast), 35% & 40% 50 Injections			Saline 18 Injections Control
	Right	Left	% Total	Right	Left	% Total	
No effect	6	3	30	11	2	26	18
1+ Sinus slowing 19 beats/min. or less	11	2	43	7	6	26	
2+ Sinus slowing 20-39 beats/min.	1	5	20	4	7	22	
3+ Sinus slowing 40 beats/min. or more	1	1	7	9	4	26	
Total	19	11	100	31	19	100	18
Sinus arrest & nodal escape	2	1		7	4		
T-wave changes				1	1		
QRS changes				1			

As demonstrated in the Table, no electrocardiographic abnormality was observed in 30% of the diatrizoate injections and in 26% of the iodopyracet injections. A slight slowing (1+), of up to 19 beats per minute, in the cardiac rate was noted in 43% of the diatrizoate group and in 26% of the iodopyracet series. A moderate slowing (2+), of between 20 and 39 beats per minute, occurred in 20% of the diatrizoate group and in 22% of the iodopyracet series. The most profound effect (3+), namely, a change in rate of 40 or more beats per minute, occurred in only 7% of the diatrizoate group, as compared with 26% of the iodopyracet series. This response was accompanied by sinus arrest for as long as 10 seconds in one case (Fig. 1*C*, *D*). Sinus arrest was followed by ventricular escape with shift of the cardiac pacemaker to the coronary sinus or to the AV node, followed by the development of nodal rhythm and irregularities in pulse rate for periods of 15 to 30 seconds (Figs. 1, 3). The rare changes in the T-wave and in the QRS complex in this latter group suggested a direct myocardial effect (Figs. 1*B*, 3*C*).

The ECG responses obtained with the use of both compounds can be explained only on the basis of vagus nerve stimulation. The duration of the responses varied directly with the intensity of the reactions elicited. The minor reactions were brief, lasting from three to six seconds. Those of greater intensity persisted from 10 to 15 seconds. In two patients 20 to 30 seconds elapsed before normal rhythm was resumed.

The vagal responses were usually similar when the same compound was used a second

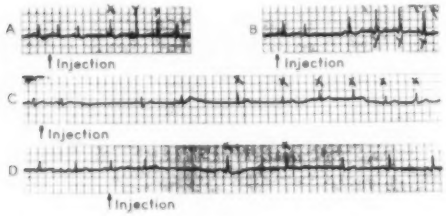

Fig. 1.—*A* and *B*, slowing of the sinus pacemaker, coronary nodal beat (*X*), and alteration in QRS complexes (*V*) after injection of 40% iodopyracet (Diodrast). *C* and *D*, sinus arrest for 10 seconds, with nodal escape beats (*X*) after injection of 40% iodopyracet.

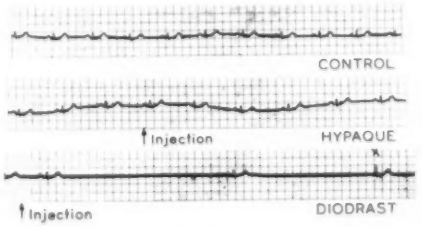

Fig. 2.—Premjection record followed by a slight sinus slowing (1+) after injection of 50% diatrizoate (Hypaque) sodium. Marked sinus slowing (3+) with nodal escape beats (*X*) after injection of 40% iodopyracet in the same patient.

Fig. 3.—*A*, control, pre-injection record. *B*, sinus slowing and nodal escape beats after iodopyracet injection. *C*, T-wave inversions 33 seconds following the iodopyracet injection.

time, although occasional variations occurred in the same subject. The reactions to iodopyracet were severer in 13 patients when the effects of both iodopyracet and diatrizoate were compared in the same subject (Fig. 2), and the effects were approximately equal in 6 patients. In only one patient was the reaction more intense with diatrizoate. As little as 3 ml. of iodopyracet was capable of producing a moderate response in one patient.

The effect of local infiltration of the carotid sinus area with procaine on subsequent intracarotid injections was evaluated in six patients. Moderate electrocardiographic reactions were observed during angiography in four patients prior to blocking the sinus and severe reactions in two. After effective block of the carotid sinus had been demonstrated by the loss of the carotid sinus reflex in five patients, repeated arterial injections failed to elicit the previous vagal responses (Fig. 4). In one patient who had an incomplete block only the slightest slowing was elicited. This would suggest that carotid-sinus procaine block interrupted the afferent impulses responsible for stimulation of the vagal centers in the medulla and explained the attendant absence of electrocardiographic changes.

The carotid body, situated at the bifurcation of the carotid artery, functions as a chemoreceptor. It is affected by alterations in the carbon dioxide and oxygen tensions of the blood, by the hydrogen ion concentration, and by drugs, such as nicotine, acetylcholine, and cyanide. Respiration, heart rate, and blood pressure are reflexly affected, through variations in the chemical composition of the blood flowing through the carotid bifurcation. The slowing of the heart is mainly due to reflex stimulation of the nucleus of the vagus nerve. The fall in blood pressure usually accompanying this phenomenon is caused by decreased

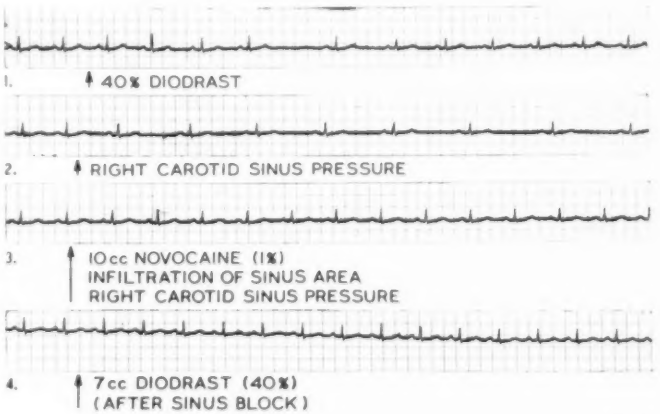

Fig. 4.—(*1*) Moderate sinus slowing after injection of iodopyracet. (*2*) Similar effect following carotid sinus pressure. (*3*) Infiltration of carotid sinus with 1% procaine hydrochloride, followed by massage, no longer elicits the sinus slowing noted in *2*. (*4*) Reinjection of iodopyracet fails to elicit the response noted in *2*.

cardiac output and by inhibition of the normal tonic discharge of the vasomotor center, leading to generalized vasodilatation and diminished peripheral resistance.[15] Since the carotid sinus is sensitive only to pressure changes, the absence of any response to saline injection in our series appears to exclude this factor. Only the chemoreceptors in the carotid body remain as the apparent source of afferent stimuli acting on the vagal centers.

When the area of the carotid sinus is anesthetized, blocking of the vagus nerve trunk at the site of infiltration may occur. Since there is a bilateral vagal supply to all supraventricular areas of the heart,[16] interrupting the function of one trunk would be insufficient to eliminate the responses noted by us. Chemical stimulation of the many cerebral centers known to effect respiratory and cardiovascular function cannot be effectively eliminated by carotid sinus block.

It is well known that elderly persons with hypertension and arteriosclerosis are especially susceptible to cardiac arrest and syncope during carotid sinus stimulation.[16] No direct evidence is available concerning unusual sensitivity of these patients to chemical stimulation of the carotid body. This group is also known for a high incidence of untoward reactions to carotid angiography. The present series of cases is too small to indicate which type of patient would be most liable to the chemotoxic responses observed.

Our results suggest that the morbidity associated with angiography may be in part produced by exaggerated slowing, irregularity, or arrest of the cardiac rhythm caused by the chemical effect of the injected material on the carotid body. Carotid sinus block with procaine should be performed before angiography in those patients in whom a fall in blood pressure or a change in heart rate and rhythm would be considered unjustifiably hazardous. Elderly persons may be safeguarded by observing electrocardiographic changes during the initial injections of the contrast medium.

Summary

Eighty carotid arteriographic studies were performed on 35 patients suspected of intracranial pathology. Serial electrocardiograms were made before, during, and after the intracarotid injection of iodopyracet (Diodrast) and diatrizoate (Hypaque) sodium to determine the cardiovascular effects of these compounds. The electrocardiographic responses obtained could only be explained on the basis of vagal stimulation and consisted chiefly of slowing of the sinus rate and sinus pauses, followed by nodal escape and the development of nodal rhythm for as long as 30 seconds. The electrocardiographic responses obtained were severer using 35% and 40% concentrations of iodopyracet than with 50% solutions of diatrizoate sodium. No response occurred with injections of saline.

Local infiltration of the area of the carotid sinus with procaine effectively eliminated the previously obtained vagal responses, suggesting that the afferent impulses responsible for stimulation of vagal centers in the medulla had their origin in the chemically sensitive carotid body.

These results indicate that the morbidity associated with this procedure may be related to the cardiovascular effects of these compounds. The area of the carotid bifurcation should be anesthetized before the performance of angiography in those patients in whom a fall in blood pressure or a change in cardiac rate or rhythm would be dangerous.

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REFERENCES

1. Utterback, R. A., and Haymaker, W.: Fatal Complications from the Use of Diodrast for Cerebral and Thyroid Angiography: Clinical-Pathological J. Nerv. & Ment. Dis. 116:739-759, 1952.

2. Broman, T., and Olsson, O.: Experimental Study of Contrast Media for Cerebral Angiography with Reference to Possible Injurious Effects on the Cerebral Blood Vessels, Acta radiol. 31:321-334, 1949.

3. Bassett, Rogers, and Cherry: Personal communication to Foltz, Thomas, and Ward.[4]

4. Foltz, E. L.; Thomas, L. B., and Ward, A. A., Jr.: Effects of Intracarotid Diodrast, J. Neurosurg. 9:68-82, 1952.

5. Browne, K. M., and Stern, W. E.: Experimental Observations Concerning Cerebral Angiography, A. M. A. Arch. Neurol. & Psychiat. 71: 477-487, 1954.

6. Gordon, A. J.; Brahms, S. A.; Megibow, S., and Sussman, M. L.: An Experimental Study of the Cardiovascular Effects of Diodrast, Am. J. Roentgenol. 64:819-830, 1950.

7. Brown, A. S.: Circulatory Disturbances During Cerebral Angiography, Anæsthesia 10:346-358, 1955.

8. Verbrugghen, A.: Complications of Iodopyracet (Diodrast) Arteriography, A. M. A. Arch. Neurol. & Psychiat. 71:518-519, 1954.

9. Sedzimer, C. B.: Towards Safer Angiography, J. Neurosurg. 12:460-467, 1955.

10. Sutherland, D. L.; Kite, W. C., Jr.; Roach, J. F., and Campbell, E.: A Note on the Use of 25% Iodopyracet (Diodrast) in Cerebral Angiography, J. Neurosurg. 12:223-225, 1955.

11. Segelov, J. N.: Safe Angiography, J. Neurosurg. 13:567-574, 1956.

12. Rigos, F. J.; Larson, C. P., and Rosenbladt, W. J.: Cardiac Arrest During Intravenous Urography, to be published; cited by Pendergrass, E. P.; Hodes, P. J.; Tondreau, R. L.; Powell, C. C., and Burdick, E. D.: Further Consideration of Deaths and Unfavorable Sequelae Following the Administration of Contrast Media in Urography in the United States, Am. J. Roentgenol. 74:262-287, 1955.

13. Wicklbom, I.: Death Following Contrast Injection into the Thoracic Aorta: Case Report, Acta radiol. 38:350-354, 1952.

14. Horger, E. L.; Dotter, C. T., and Steinberg, I.: Electrocardiographic Changes During Angiocardiography, Am. Heart J. 41:651-655, 1951.

15. Wright, S.: Applied Physiology Ed. 9, New York, Oxford University Press, 1955.

16. Heidorn, G. H., and McNamara, A. P.: Effects of Carotid Sinus Stimulation on the Electrocardiograms of Clinically Normal Individuals, Circulation 14:1104-1113, 1956.

Course of a Neurotropic Toxin to the Central Nervous System

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There has probably been more research on the pathway of tetanus toxin to the central nervous system than on that of any other neurotropic agent. In spite of this, considerable controversy exists as to whether some element of the peripheral nerve or the vascular stream constitutes the primary route.

The present investigation was undertaken in the hope of resolving some of the problems relating to the communications between the periphery and the central nervous system. Although tetanus toxin was the only agent studied, the results may suggest likely routes for other neurotropic substances.

Experimental Procedures

A highly inbred Sprague-Dawley strain of adult rats was used in all experiments. The minimum lethal dose (M. L. D., least amount of tetanus toxin which would kill all animals) was determined by Fedinec and Matzke[1] to be 0.0015 ml/100 gm. of body weight of a 1:400 dilution of the toxin injected intramuscularly. The dose of antitoxin was, in all cases, calculated to be 20 times that of the amount necessary to neutralize the volume of toxin administered. All injections were made with a microsyringe through a 30- or 33-gauge needle.

In three groups of controls, consisting of 15 animals each, 2 M. L. D.'s of tetanus toxin were injected into the following sites: right gastrocnemius muscle, perineurium of the right sciatic nerve and the saphenous vein.

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The procedures utilized on all animals are recorded in Tables 1 to 4.

The epineurium was removed from a segment of 1 cm. by making a shallow circular incision with an iridectomy knife through the epineurial connective tissue of the nerve. The cut ends were secured with iridectomy forceps and the epineurium peeled off. Part of the perineurium was removed from the large fascicles of the nerve in the same manner. In addition, small fascicles were teased apart by gently breaking down the remaining connective tissue septa. Twenty-four hours was allowed for recovery before the toxin was injected. These procedures did not interfere with the normal structure and function of the nerve fibers, as determined by microscopic examination and strength of muscle response following direct electrical stimulation of the nerve.

In Groups 3 through 15, in which the sciatic nerve was the only intact nerve to the extremity, all other nerves were sectioned 10 days before the toxin was administered. In Group 1 the toxin was injected 200 to 375 days following nerve suture. The toxin was administered 10 days after crushing the sciatic nerve in Groups 2 and 7 through 10.

The gastrocnemius was the site used for the intramuscular injection of toxin in Groups 3 through 10. In all cases 2 M. L. D.'s were administered, except in Groups 13 through 15, where the dose was 0.5 M. L. D. The antitoxin was given intravenously at the time the toxin was injected. This was done in order to insure the elimination of all circulating toxin. All epineurial and perineurial injections of toxin were directed toward the peripheral portion of the nerve trunk.

Results

Controls (Table 1).—The latent period i. e., time elapsing between injection and appearance of the first symptoms, was 18 to 26 hours for the intramuscularly and perineurially injected controls. The first sign was spasticity of the musculature of the injected extremity. There followed progressive involvement of the musculature of

TABLE 1.—*Animals Not Operated upon Except for Sciatic Nerve in Groups 1 and 2*

Group	No. of Animals	Sciatic Regenerated	Sciatic Crushed	Injection Site of Toxin	Local Tetanus, Hr.	Blood-Borne Tetanus	Death, Hr.
Control	15	—	—	I. M.	24.5±2.1	—	71.1±2
Control	15	—	—	Perineurium	25±3.1	—	70.6±2.5
Control	15	—	—	I. V.	—	59±2.8	69.3±3
1	30	Yes	—	Perineurium	33±3.5	—	135±18.9
2	30	—	Yes	Perineurium	34±2.2	—	214.9±28.3

the body in a segmental manner. The tail next became rigid, followed by spasticity of the back muscles, resulting in lumbar scoliosis. The opposite extremity, thoracic musculature, forelimbs, and muscles of the head and neck were involved, in that order. Death occurred in 68 to 74 hours following injection, apparently due to respiratory failure.

The term "local" tetanus is used here to designate the condition in which a specific group of muscles at or near the site of inoculation first shows signs of tetanus, followed by a progressive involvement of adjacent muscular groups. If not arrested by use of antitoxin, the condition terminates in general tetanus and death.

The initial signs following intravenous injection were trismus and immobility of the vibrissae. The latent period was 54 to 62 hours and the survival time 64 to 72 hours. At the time of death only the axial and head muscles exhibited spastic contraction. The extremities were rarely involved. This condition is referred to as "blood-borne" tetanus.

Group 1 (sciatic nerve regenerated; Table 1).—At the time of injection of the toxoid into the distal segment of the regenerated sciatic nerve, the response to nociceptive and direct electrical stimulation was near normal. The number of fibers in the distal segment ranged from 3,800 to 7,800, which compares favorably with an average of 6,000 in the normal sciatic nerve. The fibers, however, were of a smaller diameter, and considerable connective tissue was present at the site of the suture.

The first sign of local tetanus appeared in 30 to 36 hours and death in 116 to 154 hours. Except for the longer latent period and survival time, the pattern was identical with that in the intramuscularly injected controls.

Group 2 (sciatic nerve crushed; Table 1).—Local tetanus appeared in the animals with a crushed sciatic nerve in 29 to 39 hours, and death occurred in 161 to 242 hours following injection of toxin distal to the crushed area. The pattern of local tetanus appearing in the muscles with an intact nerve whose segmental origin is adjacent to the origin of the destroyed fibers was similar to that in the controls except for the prolonged latent period and survival time.

Microscopic sections through the crushed area revealed marked proliferation of the connective tissue. No intact fibers were found in sections of the nerve distal to the crushed area.

Groups 3 Through 6 (denervated extremity, sciatic nerve intact, toxin intramuscularly; Table 2).—All animals in Groups

TABLE 2.—*Denervated Extremity; Sciatic Nerve Intact; Toxin Intramuscularly*

Group	No. of Animals	Epineurium Only Removed	Epi-Perineurium Removed	Antitoxin (I. V.)	Local Tetanus, Hr.	Blood-Borne Tetanus	Death, Hr.
3	10	Yes	—	—	26±2.1	—	105.6±8.2
4	10	Yes	—	Yes	27.8±1.2	—	Survived
5	10	—	Yes	—	—	99.5±11.3	165.7±24
6	10	—	Yes	Yes	—	—	Survived

TABLE 3.—*Denervated Extremity; Sciatic Nerve Crushed; Toxin Intramuscularly*

Group	No. of Animals	Epineurium Only Removed	Epi- and Perineurium Removed	Antitoxin (I. V.)	Local Tetanus, Hr.	Blood-Borne Tetanus	Death, Hr.
7	10	Yes	--	--	70.4±2	92.8±4	115.6±7
8	10	Yes	--	Yes	82.4±12.6	--	Survived
9	10	--	Yes	--	--	89.2±1.2	117±9.2
10	10	--	Yes	Yes	--	--	Survived

3 and 4, in which only the epineurium was removed, developed local tetanus in 24 to 30 hours. Those protected by intravenous antitoxin (Group 4) developed symptoms which did not advance beyond the stage of lumbar scoliosis, and all survived. The period necessary for complete recovery was not determined, since the animals were killed 20 days after injection. The unprotected animals died in 95 to 120 hours. The pattern of appearance of local and general signs was the same as in the intramuscularly injected controls except for the prolonged survival time.

If most of the perineurium was also removed (Groups 5 and 6), blood-borne tetanus resulted unless the animals were protected with antitoxin (Group 6), in which case no symptoms of tetanus appeared. Blood-borne signs appeared in 91 to 127 hours and death in 145 to 190 hours. The symptoms were comparable to those seen in the intravenously injected controls except for the prolonged latent period and survival time.

Groups 7 Through 10 (denervated extremity, sciatic nerve crushed, toxin-intramuscularly; Table 3).—In animals with only the epineurium removed distal to the crushed area (Group 7) the latent period for local tetanus was 68 to 75 hours and the survival time 98 to 127 hours. The prolonged latent period may be explained in part by the fact that the first detectable signs following complete denervation of the extremity involve the musculature of the lumbar and tail region. Blood-borne signs were superimposed on those of local tetanus 2 to 10 hours after the appearance of lumbar scoliosis. Microscopic sections through the crushed and peeled areas of the nerve revealed a large amount of connective tissue. In the animals (Group 8) that received antitoxin the latent period of local tetanus was 61 to 96 hours. Signs did not advance beyond the stage of tail involvement, nor did signs of blood-borne tetanus appear.

Animals with both epineurium and perineurium removed and no antitoxin (Group 9) developed symptoms of blood-borne tetanus in 88 to 92 hours following injection and died in 100 to 127 hours. All of the animals in the group (10) given antitoxin survived without showing any signs.

Groups 11 Through 15 (denervated extremity, sciatic nerve and its sheaths intact; Table 4).—In the animals (Group 11) receiving 2 M. L. D.'s in the epineurium and no antitoxin local tetanus appeared in 28-31 hours and blood-borne signs in 70-99 hours. Death occurred in 166 to 265 hours. Those protected with antitoxin (Group 12) developed only the initial signs of local tetanus, at 30-35 hours. When a sublethal dose

TABLE 4.—*Denervated Extremity, Sciatic and Its Sheaths Intact*

Group	No. of Animals	Injection Site and Dose of Toxin	Antitoxin (I. V.)	Local Tetanus, Hr.	Blood-Borne Tetanus	Death, Hr.
11	5	Epineurium 2 M. L. D.		30±1.5	80.2±9.8	224.6±25.4
12	5	Epineurium 2 M. L. D.	Yes	32±2.6	--	Survived
13	5	Epineurium 0.5 M. L. D.		46.2±1.4	--	Survived
14	5	Epineurium 0.5 M. L. D.	Yes	95±2.4	--	Survived
15	5	Perineurium 0.5 M. L. D.	Yes	37.4±0.4	--	Survived

was administered in the epineurium (Group 13), all animals developed local tetanus, but the first signs were delayed up to 45-49 hours. The latent period was prolonged up to 89-101 hours when antitoxin was given (Group 14). In the last group two of the five animals developed no symptoms. If a sublethal dose was injected into the perineurium and antitoxin inoculated intravenously (Group 15), the latent period of local tetanus was reduced to 36-38 hours. In addition, the signs advanced to lumbar and thoracic involvement.

Comment

Local signs, followed by progressive segmental involvement, general tetanus, and death, result from the intramuscular injection of a lethal dose of tetanus toxin. This pattern is not altered when all circulating toxin is eliminated by intravenous antitoxin; however, if the dose of antitoxin is large, the progress of the symptoms may be halted short of death. These results, which suggest a nerve pathway for the toxin, confirm those of a number of other investigators. D'Antona [2] was able to destroy this pattern by sectioning the nerve to the injected extremity at the time the toxin was administered. His animals developed symptoms similar to those receiving intravenous toxin. Baylis et al.[3] prevented the appearance of general tetanus by sectioning the spinal cord. Furthermore, Friedemann, Hollander, and Tarlov [4] and d'Antona [5] showed that intravenous antitoxin is 20 to 80 times as effective against intravenous toxin as against the same amount of toxin injected intramuscularly.

Matzke and Fedinec [6] and Schellenberg and Matzke,[7] utilizing parabiotic rats with and without a regenerated crossed sciatic nerve, suggested that tetanus toxin can pass directly from one animal to the central nervous system of the other, primarily by way of a crossed nerve trunk. Their results, however, did not indicate what element of the peripheral nerve constituted the pathway for the toxin.

Baylis et al.[8] were able to delay the onset of local tetanus by sclerosing the nerve. They conclude that the fluid in the connective tissue spaces of the nerve trunk is the carrier of the toxin. Sclerosing the nerve results in a heavy deposit of connective tissue, blocking the tissue spaces but leaving the nerve fibers intact. Consequently, the rate of ascent of the toxin is slowed. The present study supports these findings, since the latent period was longer than in the controls whenever the sciatic nerve was traumatized by crushing, suturing, or removing sheaths. All of these procedures resulted in deposition in the nerve of a large amount of connective tissue at the operative site. If the latent period was prolonged excessively, blood-borne symptoms were superimposed on the local signs unless antitoxin was administered.

Two distinct layers of connective tissue can be seen in the sciatic nerve of the rat. The epineurium is the outermost and surrounds the entire nerve. The perineurium forms a firm sheath around the individual fascicles. The present investigation shows that the perineurium must be intact for local tetanus to appear. If this sheath is removed and the remaining septa teased open, only blood-borne signs appear after intramuscular injection of toxin unless antitoxin is administered. It should follow from this that if the toxin is injected into the perineurial and endoneurial tissue spaces, local tetanus will appear, whereas blood-borne tetanus will follow epineurial injection. The results of these experiments support the former but not the latter statement. Even sublethal doses in the epineurium resulted in local tetanus, although the latent period was much longer than that following perineurial administration. Blood-borne tetanus does appear shortly after local signs when a lethal dose is injected into the epineurium. This may be explained on the basis of diffusion of the toxin from the epineurium into the perineurium, as well as into the blood.

Crushing the nerve results in the destruction of the nerve fibers but leaves the connective tissue sheaths intact. This pro-

cedure, when followed by injection of toxin into the denervated muscles, did not prevent the appearance of local tetanus in adjacent muscles whose intact innervation came from some of the same segments that supplied fibers to the crushed nerve. The presence of a crushed area prolonged the latent period of local tetanus and resulted in blood-borne signs being superimposed on those of local tetanus. Intravenous antitoxin prevented the appearance of the former.

It is apparent from these and other studies that toxin may be transported by the blood and result in a characteristic syndrome, referred to here as blood-borne tetanus. This syndrome appears after intravenous injection of the toxin and after intramuscular administration only if the nerve pathway is blocked by cutting or sclerosing the nerve or opening the perineurial tissue spaces. No agreement has been reached as to the portal of entry of the toxin from the blood into the central nervous system. D'Antona[5] believes that the toxin passes from the blood, through the motor end-plates and peripheral nerves, to the brain and cord. Abel, Firor, and Chalian[9] state that the hematoencephalic barrier is permeable to tetanus toxin, whereas Friedemann, Hollander, and Tarlov[4] conclude that negatively charged protein molecules, such as those of tetanus toxin, cannot cross the barrier. Investigations are under way to clarify further the relationship of the vascular stream and tissue spaces to the central nervous system. The experiments are designed to determine whether the hematoencephalic barrier is impermeable to the toxin and to apply the same techniques to the study of other neurotropic agents. Other work is designed to study the site and mechanism of action of tetanus toxin.

Summary

Intravenous tetanus antitoxin in a dose 20 times that necessary to neutralize the injected toxin will prevent blood-borne tetanus, but not local signs, in rats.

Local tetanus appears in the absence of epineurial sheaths, whereas blood-borne signs result if most of the perineurium is removed and part of the endoneurial tissue spaces teased open. Intravenous antitoxin prevents the appearance of the blood-borne, but not the local in tetanus.

The destruction of nerve fibers to the injected muscles does not prevent the appearance of local tetanus in adjacent muscles with intact nerves arising from some of the same segments which gave origin to the degenerated fibers. If the epineurium is also removed, local signs still appear, whereas only blood-borne signs result if the perineurium is partially removed. The latter signs do not appear in the presence of antitoxin.

Toxin injected into the epineurium results in blood-borne tetanus, as well as local tetanus. Only local tetanus follows perineurial injection. The latent period of local tetanus is shorter after perineurial injection than after epineurial administration of toxin. The presence of a peripheral nerve barrier localized in the perineurium is suggested.

Scar tissue resulting from cutting or crushing a nerve increases the latent period of local tetanus, prolongs the survival time, and facilitates the development of blood-borne tetanus.

The possibility that tetanus toxin may reach the central nervous system via the tissue spaces in the perineurium is discussed.

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REFERENCES

1. Fedinec, A. A., and Matzke, H. A.: The Role of Tissue Spaces and Nerve Fibers in the Spread of Tetanus Toxin in the Rat, Kansas Sc. Bull. 38: 1439, 1958.

2. d'Antona, D.: La propagation de la toxine tétanigue par la voie nerveuse démontrée par la résection des nerfs chez les animaux en état d'immunité, Rev. immunol. 13:128, 1949.

3. Baylis, J. H.; Joseph, T.; Mackintosh, T.; Morgan, R. S., and Wright, G. P.: Effect of Transection on the Ascent of Tetanus Toxin in the Rabbit's Spinal Cord, J. Path. & Bact. 64:47, 1952.

4. Friedemann, U.; Hollander, A., and Tarlov, I. M.: Investigations on the Pathogenesis of Tetanus, J. Immunol. 40:325, 1941.

5. d'Antona, D.: Le tétanos; synthèse théorique et pratique de nos principales connaissances, Rev. immunol. 15:93, 1951.

6. Matzke, H. A., and Fedinec, A. A.: The Spread of Tetanus Toxin Along the Sciatic Nerve of the Rat, Anat. Rec. 121:335, 1955.

7. Schellenberg, D. B., and Matzke, H. A.: The Development of Tetanus in Parabiotic Rats, J. Immunol. 80:367, 1958.

8. Baylis, J. H.; Mackintosh, J.; Morgan, R. S., and Wright, G. P.: Effect of Sclerosis of the Nerve Trunk on the Ascent of Tetanus Toxin in the Sciatic Nerve of Rabbits and on the Development of Local Tetanus, J. Path. & Bact. 64:33, 1952.

9. Abel, J. J.; Firor, W. M., and Chalian, W.: Researches on Tetanus: IX. Further Evidence to Show That Tetanus Toxin is Not Carried to the Central Nervous System by Way of the Axis Cylinders of Motor Nerves, Bull. Johns Hopkins Hosp. 63:379, 1938.

Central Pontine Myelinolysis

A Hitherto Undescribed Disease Occurring in Alcoholic and Malnourished Patients

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In the course of our studies of the neuropathology of alcoholism, which were begun at the Neurological Unit, Boston City Hospital, and have continued in the laboratories of the Neurology Service, Massachusetts General Hospital, two of us (R. D. A. and M. V.) observed three, perhaps four, cases in which the myelin sheaths of all the nerve fibers in the central part of the basis pontis had been destroyed in a single, large, symmetric focus. The nerve cells and axis cylinders were spared for the most part, and the blood vessels were patent and unaffected. There were no signs of inflammation in or near the lesion. The disease had occurred on a background of alcoholism and malnutrition; in the two cases with the largest lesions, it had manifested itself clinically by a pseudobulbar palsy and quadriplegia, leading to death in about 13 and 26 days. In the other two cases there were no symptoms referable to the lesions, presumably because of their small size.

The disease which is to be described does not resemble any of the known varieties of demyelination. It is unique both in its distribution and in the apparent character of the pathologic process and resulting morbid change. We have searched the medical literature in order to determine whether or not this condition was known to other neuropathologists but have failed to discover a single case of this type. These considerations have encouraged us to present our cases in some detail and to attempt an analysis of the main features of this disease.

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Report of Cases

CASE 1.—*A chronic alcoholic entered the hospital with lobar pneumonia and delirium tremens. His symptoms were improving when, over a two-day period (9th to 11th hospital day), he developed flaccid quadriplegia, weakness of the face and tongue, and inability to speak and swallow. Death ensued on the 22d hospital day, and postmortem examination disclosed a symmetric destruction of the myelinated sheaths of the basis pontis, with relative intactness of the nerve cells and axis cylinders.*

A 38-year-old man was admitted to the Second (Harvard) Medical Service of the Boston City Hospital on May 5, complaining of tremulousness and hallucinations, of recent onset. The patient was a confirmed alcoholic who had been drinking steadily for many years. In addition, there were intermittent periods in which he would greatly increase his alcoholic intake, and twice in the past, after such an episode, he had been hospitalized for delirium tremens.

For two weeks before his final illness the patient had been drinking particularly heavily, and in the last three or four days of this period he had been unable to eat and vomited several times. On the day before admission he became very tremulous and began to see "impossible things." He feared that he was losing his mind and asked for protection from the police, who, in turn, brought him to the hospital. The patient also gave a history of a recent cold, with cough and pain in the left chest.

On admission to the hospital the patient appeared seriously ill. He was dehydrated; his respirations were rapid and gasping, 45 per minute; the temperature was 102 F, pulse 130 per minute, and blood pressure 90/60. The important physical findings were in the lower lobe of the left lung, where dullness to percussion, increased bronchial breath sounds with egophony, and fine inspiratory rales were detected. Although the patient was restless

and hallucinating, he was able to recount the major events of his medical history. He moved all his extremities well, but deep reflexes were absent at the knees and ankles.

Ancillary examinations at the time of admission disclosed the following: urine normal; hemoglobin, 12.5 gm. %; WBC, 11,000, with 96% polymorphonuclear cells; blood Hinton test, negative; NPN, 55 mg. %. Diplococcus pneumoniae Type 5 was cultured from both the blood and throat; x-ray of the chest showed consolidation of the left lower lobe and a fracture of the fourth left rib in the anterior axillary line. The spinal fluid was under an initial pressure of 135 mm. H_2O and contained 1800 RBC (traumatic), 7 WBC (4 lymphocytes and 3 polymorphonuclear cells), 28 mg. % of protein, and 73 mg. % sugar. The colloidal gold curve was flat. Spinal fluid culture showed no growth.

The patient was given oxygen, and penicillin, 400,000 units initially and 200,000 units every two hours thereafter. He received infusions of 3000 ml. of fluid daily, including 1500 ml. of isotonic saline, 300 gm. of carbohydrate and at least one ampule of Berocca-C.*

For the first two or three days the patient was alert and able to take small amounts of food by mouth. With adequate hydration the NPN fell to 27 mg. %. On the fourth hospital day he became tremulous and confused. On the fifth day his temperature rose to 105 F and his WBC to 18,000 per cubic millimeter. It was felt at this time that the patient was experiencing some difficulty in swallowing and talking, but these difficulties were attributed to his delirium. The medication was changed to intravenous chlortetracycline (Aureomycin) hydrochloride, 500 mg. daily, and over the next few days the temperature fell to 101 F and the pneumonic process seemed to be resolving. On the seventh day the patient's neurologic status was improved; in particular, he moved his arms and legs well. By the ninth day, however, a definite difficulty in moving the limbs and also in swallowing was noted. On the following day there were no spontaneous movements and his limbs were flaccid; he was unable to swallow, although he was still able to close his mouth. On the 11th day it was noted that he did not react to painful stimuli; the corneal reflexes were still present. His temperature rose again to 103 F, although there were no additional physical findings. An x-ray examination showed satisfactory resolution of the pneumonic process. The electrocardiogram at this time suggested potassium depletion (Q-T interval, 0.35 second); the serum potassium was 3.1 mEq/liter. However, the intravenous administration of 30 mg. of potassium chloride did not change his neurologic state.

On the 12th hospital day neurologic examination disclosed the following: The patient was conscious and moved his eyes and opened and closed his eyelids to command. The optic fundi were normal. The pupils were round, regular, and equal, 3 mm. in diameter, and reacted well to light and on convergence. The extraocular movements were full, and there was no nystagmus. The corneal reflexes were present but of less than normal briskness. The patient could open and close his mouth, but no other facial movement was possible. He was unable to speak, swallow, or move his tongue. The limbs were flaccid and almost completely paralyzed. Slight adduction of one or the other arm or leg was evoked by strong supraorbital pressure. Respirations were largely diaphragmatic, the intercostal muscles being retracted with each inspiration. The biceps and triceps reflexes were of average briskness and equal. No deep reflexes could be obtained at the wrists, knees, or ankles. The plantar responses were bilaterally extensor. The patient did not respond to pinprick anywhere over his body. A lumbar puncture on the 12th day showed the spinal fluid to be under an opening pressure of 65 mm. H_2O. There were no cells, and the total protein was 24 mg. %. Culture showed no growth.

By the 14th day there was some return of reflex activity in the legs. Otherwise there was no change until the final day of his illness, when he could no longer follow objects with his eyes. The corneal reflexes disappeared. A chest film showed a diffuse mottled density throughout both lung fields. Respirations became shallow and gasping in quality, and the patient died, apparently of respiratory arrest, on the 22d hospital day.

Pathologic Findings.—Permission was granted for examination of the nervous system only. The brain and spinal cord were studied after formalin fixation. The leptomeninges were thin and transparent. There was a slight degree of cerebral convolutional atrophy. The major blood vessels were free of atherosclerosis; the vertebral and basilar arteries particularly were of normal size and appearance and filled completely when injected with a colored liquid. The external surface of the pons was soft. On section of the brain, several portions of the cerebral cortex, especially in the parietal lobes, were swollen and specked with congested blood vessels. The centrum ovale, basal ganglia, and midbrain showed no gross lesions. The entire basis pontis, with the exception of the most caudal portion, was of gravish color

* Berocca-C (Hoffmann-La Roche, Inc.). Each 2 cc. contains thiamine hydrochloride, 10 mg.; riboflavin, 6 mg.; nicotinamide, 80 mg.; pyridoxine hydrochloride, 6 mg.; Panthenol (equivalent to 6 mg. calcium pantothenate), 6 mg., and ascorbic acid, 100 mg., with 3% gentisic acid ethanolamide as a preservative.

Fig. 1 (Case 1).—Rostral pons, showing sharply demarcated symmetric focus of demyelination in basis. Lovez myelin stain.

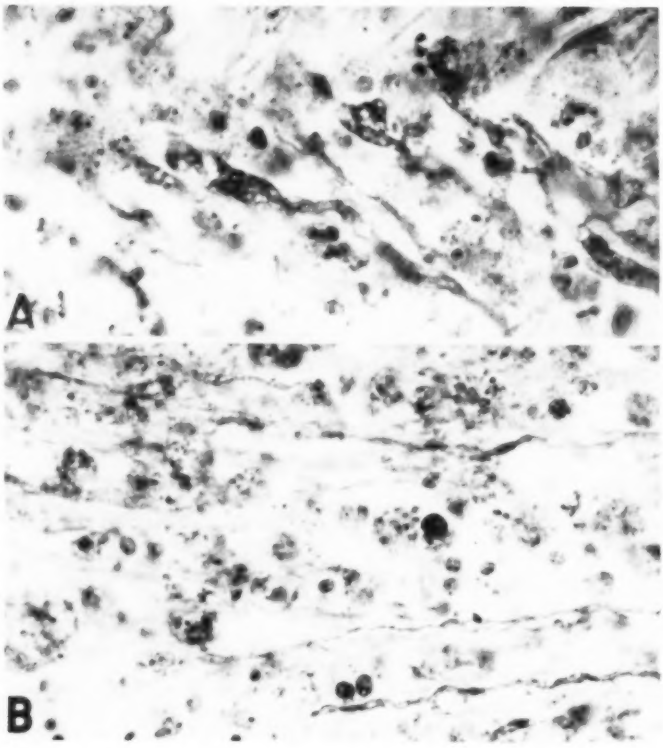

Fig. 2 (Case 1).—*A*, edge of pontine lesion, showing swollen, vacuolated, and fragmented myelin sheaths. *B*, center of lesion, containing pale remnants of fine myelin sheaths. In both sections there are numerous macrophages stuffed with hematoxyphilic granules. Lovez myelin stain.

and unusually soft. The cerebellar peduncles, cerebellum, medulla, and spinal cord were grossly normal.

The pons presented a remarkable appearance. A symmetric, sharply demarcated area of pallor was seen in the myelin-stained sections, extending through the middle and upper pons (Fig. 1). Almost the entire basis pontis was affected, with the exception of a superficial rim ventrally. Superiorly, the lesion barely extended into the tegmentum to involve the most inferomesial portions of the medial lemnisci. Laterally, fibers of both trigeminal nerves were involved as they entered the lesion. The cerebellar peduncles were completely spared, as were the lateral lemnisci, the mesencephalic tracts of the trigeminal nerves, the medial longitudinal fasciculus, the central tegmental tracts, and the major portions of the medial lemnisci. The boundary of the lesion was sharply defined but irregular, and there were numerous narrow extensions into the surrounding parenchyma. These extensions bore no relationship to venules. Bundles of myelinated fibers entering the lesion became abruptly thinned and pale. Some small vacuolated fibers of irregular caliber could be followed for a millimeter or two into the lesion, and, at the margin of the lesion, many of the myeline sheaths were greatly swollen and vacuolated or fragmented into round or oval particles (Fig. 2*A*). In horizontal sections of the pons, both the longitudinally and the horizontally oriented fibers (i. e., corticopontine, corticospinal, pontocerebellar, and trigeminal) were indiscriminately affected. Scattered throughout were many remnants of abnormally pale myelin sheaths of very small caliber, as well as numerous macrophages stuffed with fine hematoxyphilic granules (Fig. 2*B*). The largest of these macrophages were found at the periphery of the lesion.

In contrast to the advanced state of myelin destruction was the relative integrity of both nerve cells and axis cylinders. In most parts of the basis pontis the nerve cells were present in the usual numbers; in a few of the nuclear groups they were slightly reduced in number (Fig. 3*A*). Some of the nerve cells had an abnormal appearance, either of pallor and loss of cytoplasmic chromatin or of hyperchromatism. The usual

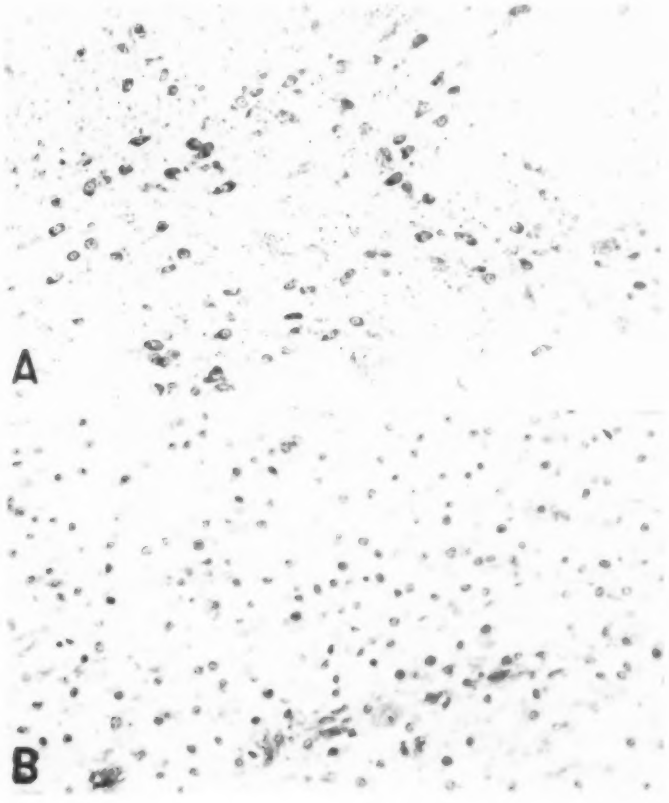

Fig. 3 (Case 1). *A*, section through pontine lesion. Nerve cells are only slightly reduced in number. Cresyl violet stain.

B, numerous fat-filled macrophages within lesion. Note binucleated forms. Hematoxylin and eosin stain.

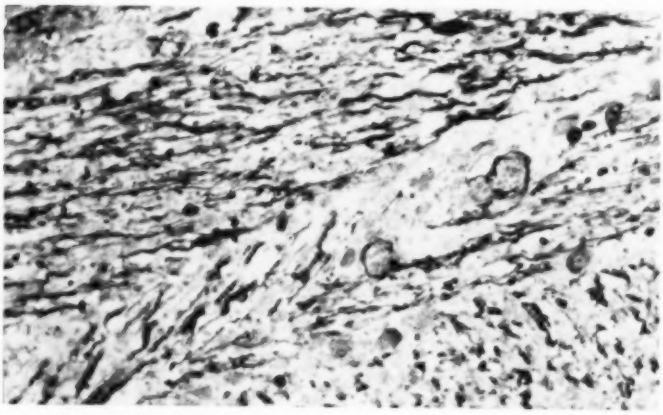

Fig. 4 (Case 1).—Relative preservation of axis cylinders within pontine lesion. Occasional fibers show bulbous swellings; all are heavily impregnated. Gros-Bielschowsky stain.

complement of axis cylinders was seen, though a few of them were fragmented and all of them tended to be heavily impregnated in Gros-Bielschowsky silver stains (Fig. 4). No oligodendrocytes could be detected in the area of demyelination. The lesion contained many large macrophages filled with fat, some with double nuclei (Fig. 3*B*). Pleomorphic microgliocytes were also present in small numbers. These phagocytic cells were unevenly distributed through all parts of the lesion. A few cells with elongated nuclei and streaming eosinophilic fibers of fine caliber were scattered throughout the lesion. These cells were readily identified in phosphotungstic acid hematoxylin stains as astrocytes. Between the lesion and the normal parenchyma, in the narrow zone containing the swollen medullated fibers, the tissue matrix appeared loosened and slightly fenestrated. Some oligodendrocytes were identifiable in this zone, though often shrunken and necrotic, and the astrocytes were hypertrophied.

There was no evidence of total tissue destruction except in a small zone on either side of the median raphe, where cavitation had occurred. Within this region several intact venules and arterioles, showing some increase in adventitial connective tissue, were seen.

Within the lesion, and beneath the floor of the fourth ventricle, blood vessels were engorged. Many of these were surrounded by small hemorrhages. These were obviously of recent origin, possibly agonal, for they had provoked no cellular reaction. The blood vessels were patent throughout the lesion, and the only alteration of their walls was a slight enlargement of endothelial cells and an increase in the number and size of adventitial histiocytes. A similar vascular engorgement was seen in the most caudal portion of the pons, which was otherwise normal (Fig. 5*A*). Inflammatory cells could not be found in any part of the lesion.

No similar lesions were found elsewhere in the nervous system. Several other abnormalities, mostly inconsequential, were noted. In the *spinal cord* there were pallor of myelin staining and a proliferation of pleomorphic microgliocytes and small astrocytes in the columns of Goll (Fig. 5*C*). In the *medulla* there were a mild gliosis beneath the floor of the fourth ventricle and widespread vascular engorgement with several small fresh perivascular hemorrhages, again without cellular reaction. These vascular changes were most prominent in the dorsal motor nuclei of the vagus. The cells of the inferior olivary nuclei contained a moderate amount of lipofuscin. The corticospinal tracts were normal both in myelin and in axis-cylinder stains (Fig. 5*B*). No significant abnormalities could be detected in the *cerebellum* or in the cerebellar peduncles. The *midbrain* was normal. In the *hypothalamus* there were several small perivascular hemorrhages in the walls of the third ventricle, and a single tiny hemorrhage was observed in one mammillary body, all unaccompanied by cellular reaction. There was no abnormality of the blood vessel walls. The hypothalamic nuclei were normal. The *basal ganglia* were of natural appearance. Random sections of the cerebral cortex, including Sommer's sector of the hippocampus, showed a slight increase in the number of astrocytes and microgliocytes. The *centrum ovale* and the *corpus callosum* contained no lesions. No abnormalities of the meninges or the ependymal lining of the ventricles were seen.

Case 2.—*A malnourished alcoholic woman was hospitalized with severe dehydration and anemia. Two weeks later she developed flaccid quadriplegia and paralysis of the bulbar and respiratory musculature. The neurologic illness evolved over a period of a week and terminated fatally from respiratory paralysis in four weeks. Postmortem examination revealed an extensive focus of demyelination in*

Fig. 5 (Case 1).—Sections through caudal pons (*A*), medulla (*B*), and thoracic cord (*C*) to demonstrate absence of descending degeneration of corticospinal tracts. There is slight pallor of the columns of Goll. Loyez myelin stain.

the basis pontis with relative preservation of the nerve cells and axis cylinders.

A 29-year-old woman was admitted to the Quincy City Hospital on Dec. 1 in a state of confusion. She was unable to provide a history of her illness, but it was learned that she had been living alone and that for at least four months she had been drinking heavily and eating poorly. For several days before her admission she had been vomiting and hiccuping persistently and had been entirely unable to eat.

On admission to the hospital the patient was uncooperative and confused. Her blood pressure was 96/50, temperature 96.5 F, pulse 75 per minute, and respirations 20 per minute. Her skin was pale and the nail beds slightly cyanotic. The tongue was dry and red, the lips dry and fissured. The heart and lungs were normal. The liver was slightly enlarged. The eye movements were full and the pupils reactive. The tendon reflexes were sluggish, but there were no pathologic reflexes.

Urinalysis showed specific gravity 1.008, albumin 2+, many pus cells and bacteria, and Escherichia coli on culture. Hemoglobin measured 76%; RBC, 3,500,000; WBC, 20,000, with 93% polymorphonuclear cells; NPN, 154 mg. %; creatinine,

7.4 mg. %; CO_2-combining power, 44 vol. %; total protein, 4.7 gm. % (albumin 3.1 gm. globulin 1.6 gm.); prothrombin activity, 67%. Gastric analysis showed free acid. Blood serology was positive. Blood and feces were negative for arsenic and mercury, and the urine was negative for lead. The electrocardiogram was normal. The chest x-ray showed a mottling of the right base.

The patient was treated with antibiotics and infusions of dextrose and saline. With an improvement in the state of hydration, the RBC dropped to 2,200,000 and the WBC to 11,200 per cubic millimeter. Within a week her urine specific gravity rose to 1.021; the NPN fell to 31 mg. % and remained normal. Concomitantly, her confusion was said to improve.

On Dec. 13 it was again noted that the patient was restless, intermittently confused, and incontinent of urine and that she complained of pain in her calves and feet. There ensued rapidly progressive weakness of the extremities, with loss of knee and ankle jerks. On Dec. 18 she was seen for the first time by Dr. Max Goldman, who supplied these clinical notes. He found the patient to be restless and agitated. She was unable to speak but could understand spoken language. The fundi appeared normal; there were no ocular palsies, and the pupils reacted to light. Sensation over the face was unimpaired. She was unable to swallow, and the gag reflex was absent. The tongue could not be protruded. All the neck muscles were weak. There was a severe flaccid weakness of all the muscles of the limbs, somewhat less in degree in the right arm and leg and perhaps less in the proximal than in the distal muscles of the limbs. All the deep reflexes were absent, and the plantar responses were abnormal, though not clearly extensor. The patient was able to perceive pinprick throughout and was able to localize the stimulus properly. She was incontinent of urine. There were no signs of meningeal irritation.

A lumbar puncture on Dec. 18 showed an initial spinal fluid pressure of 75 mm. H_2O. The fluid contained 20 RBC per cubic millimeter but no white cells, 34 mg. % protein, 57 mg. % sugar, and 720 mg. % chloride. The colloidal gold curve was flat and the serology negative. Spinal fluid examinations repeated on Dec. 23 and Dec. 27 gave essentially the same results.

The condition of the patient deteriorated progressively during the next three weeks. On Dec. 26 it was noted that she moaned constantly and exhibited emotional lability with forced crying. Her quadriplegia was now complete, and there was paralysis of the intercostal muscles as well. Knee and ankle jerks were still absent, but now the plantar responses were extensor. She was unable to perceive pinprick in any of her extremities. Respirations were shallow, 48 per minute. The patient died on the 39th hospital day.

General Pathologic Findings.—The autopsy was performed by Dr. James Nolan and Dr. O. J. Pollak. The body was emaciated, with edema of the ankles and the sacral promontory. Decubitus ulcers were present over both hips, the sacrum, and the external malleoli. The lungs were edematous and showed diffuse areas of chronic bronchitis and atelectasis. There was fatty infiltration of the liver. Microscopic examination confirmed these findings. Bronchopneumonia, atrophic gastritis, and hyperplasia of the bone marrow were also evident.

Neuropathologic Findings.—The brain and spinal cord were submitted to one of us (R. D. A.) for examination, but nerves, spinal ganglia, roots, and muscles were not available. The brain weighed 1040 gm. (after about three weeks of formalin fixation). External examination showed no abnormalities. The major blood vessels were free of atherosclerosis. A careful search of all the large intracranial arteries, particularly of the vertebral-basilar system, revealed no occlusion. On section after formalin fixation, the cerebral hemi-

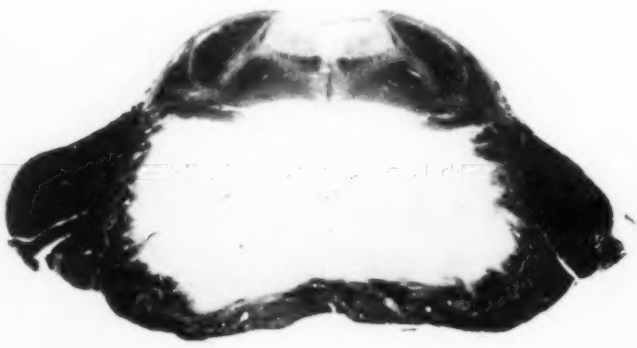

Fig. 6 (Case 2).—Section through rostral pons, showing the characteristic demyelinative lesion. Loyez myelin stain.

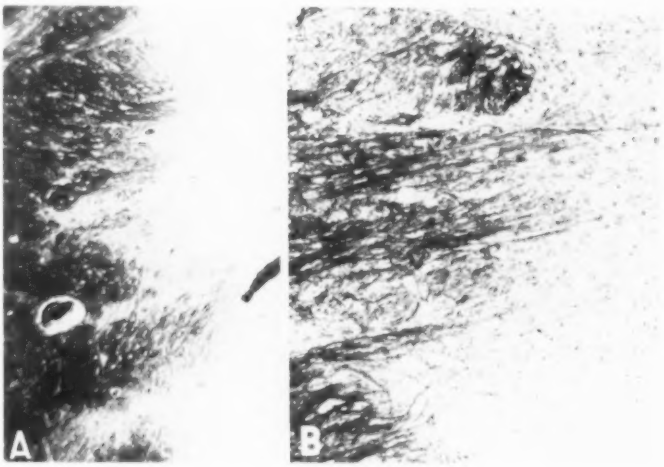

Fig. 7 (Case 2).—Sections through margin of lesion to show the serrated edge (*A*) and the abrupt transition of the myelinated fibers as they enter the lesion (*B*). Numerous macrophages are seen among the fragmenting fibers. Loyez myelin stain.

spheres and the upper brain stem appeared normal. The basal portion of the pons, along with the adjacent tegmentum, was unusually soft and gray in color, exactly like that of Case 1. This lesion was seen to involve the rostral portion of the base of the pons above the level of the abducens nuclei and was bordered anteriorly and laterally by a thin rim of white matter. The pons below the level of the abducens nuclei and the cerebellar peduncles, cerebellum, medulla, and spinal cord were grossly normal.

The important microscopic abnormalities were in the rostral part of the basis pontis. In the sections stained for myelin, a large, sharply outlined, symmetric region of pallor was seen to occupy all the central part of the basis pontis (Fig. 6). The lesion extended into the contiguous tegmentum, involving the medial portions of the medial lemnisci. The ventral rim of the basis pontis was spared, as were the lateral parts of the middle and all of the superior cerebellar peduncles, the mesencephalic roots of the fifth nerves, the lateral lemnisci, and the central tegmental tracts. The boundary of the lesion was sharply demarcated but irregular; extending from the lesion into the surrounding tissue were salients of demyelination, which bore no relation to veins (Fig. 7*A*). Fiber bundles, as they crossed the border of the lesion, became abruptly thinned out and pale and disappeared after a short distance (Fig. 7*B*). In this marginal zone, swollen myelin sheaths and myelin fragments were seen; within the body of the lesion no myelin sheaths, or even fragments, were present. The corticospinal, corticopontine, and pontocerebellar tracts were equally affected. A fine hematoxyphilic dust and larger particles still staining like myelin in a Loyez stain were present within the cytoplasm of many macrophages, particularly at the margin of the lesion, where they were intermingled with still recognizable myelin sheaths.

Nerve cells and axis cylinders within the lesion were relatively well preserved. It was our impression that the nerve cell population was slightly decreased. Occasional nerve cells were unusually pale

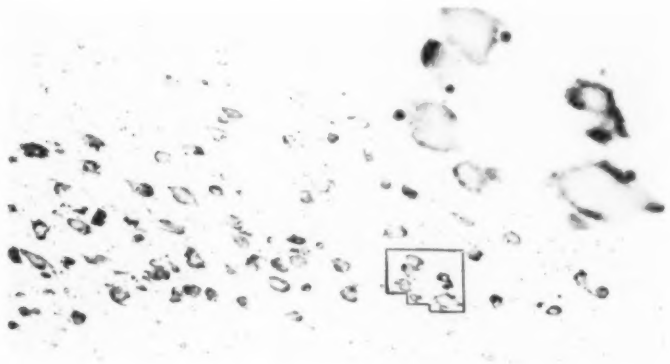

Fig. 8 (Case 2).—Relative preservation of nerve cells within lesion. Some show changes suggestive of "axonal reaction" (inset). Cresyl violet stain.

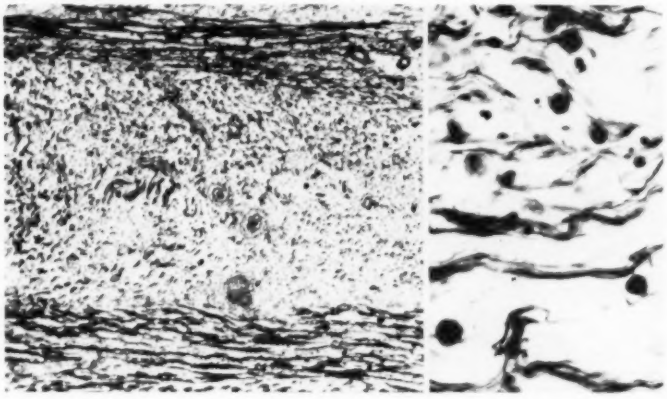

Fig. 9 (Case 2).—(Left) Relative preservation of both axial and transverse axis cylinders. (Right) Higher-power view, showing thickening and bulbous expansion of some fibers. Gros-Bielschowsky stain.

or hyperchromatic or in rare instances showed a number of changes suggestive of "axonal reaction," i. e., swelling of the cell body, eccentricity of the nucleus, loss of Nissl substance, and a glassiness of the cytoplasm (Fig. 8). The nerve fibers were heavily impregnated by the silver stain and somewhat reduced in number. Scattered ones showed abnormalities of structure, such as fragmentation, irregular thickening and tortuosity, and bulbous swellings (Fig. 9). All parts of the lesion were packed with large, often multinucleated macrophages laden with fat (Fig. 10). Pleomorphic microgliocytes were present, but in distinctly smaller numbers. The intensity of the cellular reaction was much the same throughout the body of the lesion. No oligodendrocytes were seen. Many astrocytes with fusiform nuclei and slender glial fibrils were found to be scattered throughout the lesion, somewhat more numerous peripherally than centrally (Fig. 10). These cells and fibrils were often oriented in an isomorphic fashion in both the vertical and the horizontal plane. In addition, a number of plump astrocytes could be recognized at the border of the lesion.

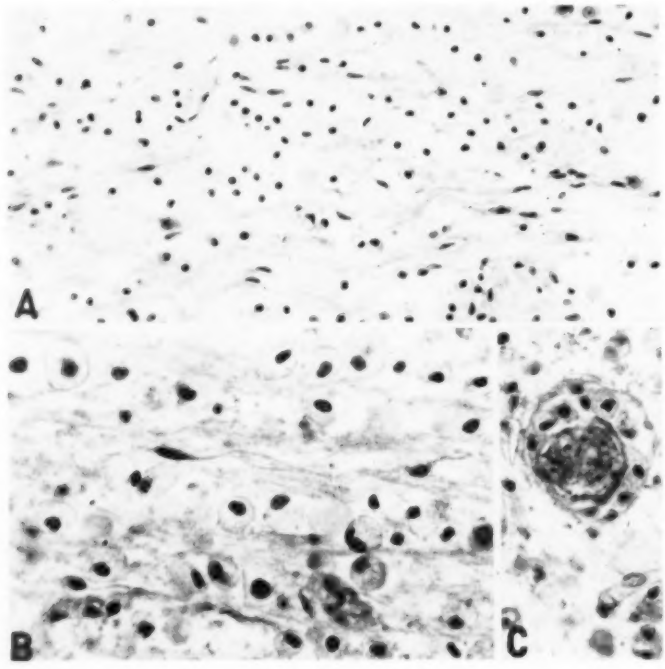

Fig. 10 (Case 2).—*A*, section through lesion, showing prominence of fat-filled macrophages; some fusiform glial cells are also present. Hematoxylin and eosin stain. *B*, higher magnification, demonstrating fusiform glial cells. Phosphotungstic acid hematoxylin stain. *C*, para-adventitial collections of macrophages within lesion. Phosphotungstic acid hematoxylin stain.

Along the median raphe in one small central focus, the tissue matrix was loose and had undergone cavitation, indicating that total tissue destruction had occurred. Infiltration of inflammatory cells was not observed either within or around the lesion, though occasionally a few lymphocytes were found in perivascular spaces. All the blood vessels were patent, and their walls showed only a slight increase in cellularity.

The changes in other parts of the nervous system were of relatively minor nature. The cells of the anterior horns of the spinal cord and of the inferior olivary nucleus and nucleus ambiguus of both sides contained a moderate amount of lipofuscin pigment. There was no evidence of degeneration of the posterior columns or of the corticospinal tracts in the medulla or in the spinal cord.

CASE 3.—*A malnourished alcoholic man developed a flaccid, areflexic weakness of the legs. He was found to have polyneuropathy and advanced pulmonary tuberculosis, of which he died three weeks later. Postmortem examination disclosed, in addition to fibrocaseous tuberculosis and evidence of polyneuropathy, a demyelinative lesion of the basis pontis.*

A 43-year-old man was admitted to the Fifth (Boston University) Medical Service of the Boston City Hospital on Feb. 6 because of weakness of his legs and difficulty in walking, of 10 days' duration. The patient had been a serious alcoholic for at least 15 years, customarily imbibing 15 to 20 glasses of ale daily. He had been relatively well until one month before admission, when he developed a persistent, productive cough and intermittent fever. Ten days before admission he noted the onset of weakness in his legs, with difficulty in walking, and had been confined to bed since that time.

The patient appeared poorly nourished and chronically ill. The temperature was 101 F; pulse 102 per minute; respirations 28 per minute. The skin was dry, dirty, and rough. The tongue was dry and beefy-red. The teeth were carious. The fundi were normal and the pupils equal and active. The neck was supple. Post-tussive rales were heard over the apex of the right lung. Examination of the heart was normal except for the presence of sinus tachycardia and a soft, blowing apical systolic murmur. Abdominal examination disclosed no abnormalities. The reflexes in the arms were equal and of normal briskness. The knee and ankle jerks could not be obtained, and the plantar responses were flexor.

An x-ray film of the chest disclosed a pneumonic density in the right upper and midlung fields, and the sputum contained tubercle bacilli. Other laboratory tests showed a normal urine; hemoglobin, 11 gm. %; WBC, 10,300, with a normal differential; sedimentation rate, 36 mm. in one hour; NPN, 32 mg. %; blood Hinton test, negative. The spinal fluid was under an initial pressure of 90 mm. H_2O, clear, and colorless, and contained 4 lymphocytes per cubic millimeter, no red cells, and a total protein of 20 mg. %. The colloidal gold curve was flat, and the serology and cultures were negative.

The patient's temperature and pulse and respiration rates remained elevated. Severe anorexia persisted, and he ate practically nothing. There was little change in his clinical picture until the 11th hospital day, when he was found in extremis. His respirations were rapid and shallow, and the pulse was very feeble. He died on the same day.

General Pathologic Findings.—The body was emaciated; over the sacral area were a number of small superficial ulcers. The apices of both lungs were the site of many firm fibrous pleural adhesions. The right upper lobe was diffusely firm and consolidated and on section showed multiple, confluent yellow caseous areas. The upper lobe of the left lung contained several apical scars; the lower lobe, many small yellow lesions. The heart and pericardium were normal. The liver was congested; the other abdominal viscera were normal. Microscopic examination of the lungs showed widespread areas of granuloma formation and caseation, characteristic of fibrocaseous tuberculosis.

Neuropathologic Findings.—The brain and spinal cord were examined after formalin fixation. The peripheral nerves were not available for gross or microscopic examination. The meninges and the large blood vessels were normal. Sections of the cerebrum showed no abnormalities. A small rounded area of gray discoloration was present in the center of the basis pontis, extending almost through the entire vertical extent of the pons. The tegmentum was not involved. Careful search of the basilar artery and its branches showed no atherosclerosis or occlusion. The remainder of the brain stem and the spinal cord were normal.

As in the previous cases, the major changes were confined to the central portion of the pons, but here the lesion was comparatively small (Fig. 11). Sections stained for myelin demonstrated a sharply demarcated focus of pallor in the center of the basis pontis. The lesion was circular in outline, measuring approximately 4 mm. in diameter. Within this area, no normal myelin sheaths could be seen, only some fragmented and extremely pale forms remaining. Throughout the lesion there were many large macrophages, the majority of which contained hematoxyphilic granules. Axis cylinders were markedly reduced in number in the very center of the lesion, but in the rest of the demyelinated area they appeared to be present in normal numbers; they were heavily impregnated by the silver stain (Fig. 12*A*). Abnormalities, such as diffuse

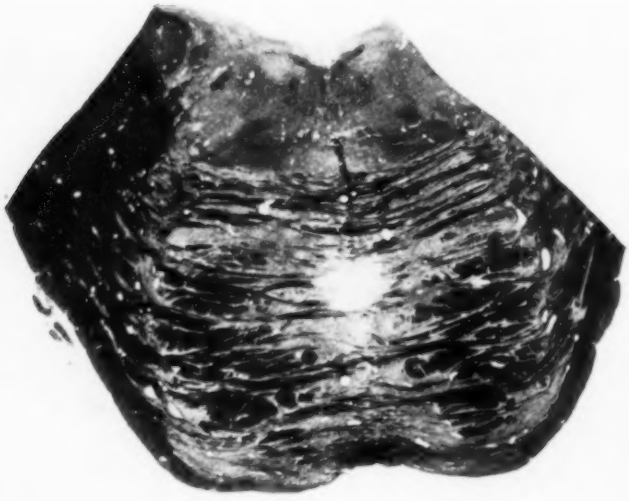

Fig. 11 (Case 3).—Small, symmetric focus of demyelination in the center of the pons. Loyez myelin stain.

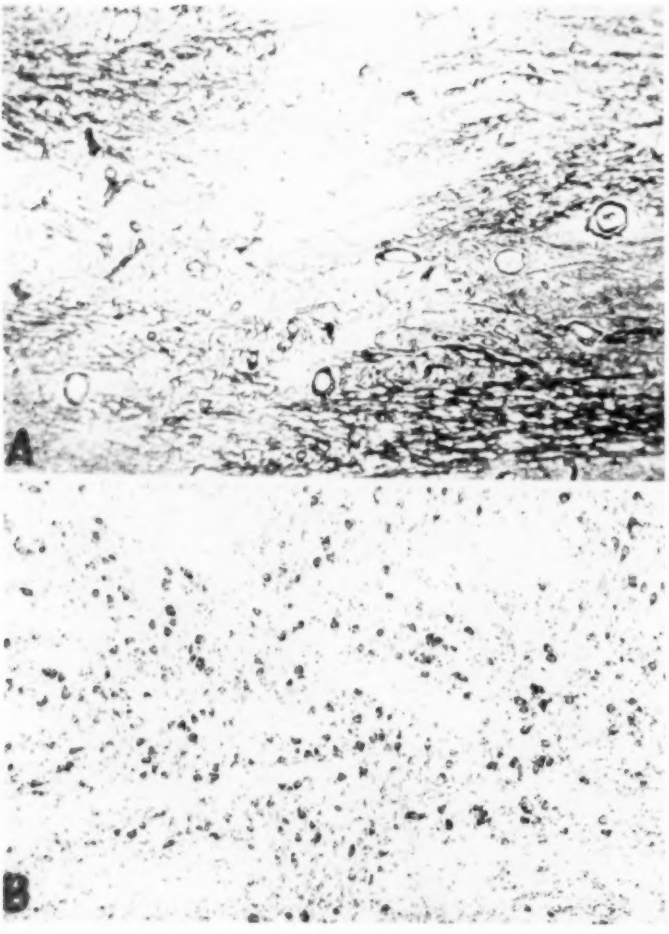

Fig. 12 (Case 3).—*A*, almost complete destruction of axis cylinders in the center of the lesion and heavy impregnation of remaining fibers. Gros-Beilschowsky stain.

B, intact nerve cells. Cresyl violet stain.

or irregular thickening, were common, and a few fibers were fragmented. Nerve cells were normal in number and appearance throughout the lesion (Fig. 12*B*). Well-developed, fat-filled macrophages and pleomorphic microgliocytes were seen in all portions of the lesion, the former being much more prominent. A few fusiform astrocytes with well-formed fibrils were seen, similar to those in the other cases. In addition, there were some plump astrocytes and a scattering of shrunken and necrotic oligodendrocyte nuclei in the periphery of the lesion. Inflammatory cells were conspicuously absent. Engorged capillaries and venules were prominent both within and surrounding the lesion. The blood vessels were patent and showed only a slight enlargement of the endothelial cells and some increase in adventitial connective tissue.

Several changes of a different nature were observed in other parts of the nervous system. In the *mammillary bodies* there were loosening of the tissue matrix, an increase in the number and size of the astrocytes, and evidence of a multiplication of microgliocytes. Nerve cells and blood vessels were largely unaffected. Similar foci of tissue alteration and glia-cell proliferation were present in the walls of the third ventricle, the medial nuclei of the *thalamus*, and the supramammillary commissure. In the *third nerve nuclei*, particularly in their central portions, there was loss of nerve cells and proliferation of astrocytes and microgliocytes. There was also a prominent gliosis in the periaqueductal gray matter and, to a less extent, in the *red nucleus*. These lesions were considered characteristic of Wernicke's disease of long standing. Throughout the *cerebral cortex* and in the *dentate nuclei* astrocytes were prominent. In the lumbar enlargement of the *spinal cord* anterior horn cells had the typical appearance of axonal reaction. A scattering of astrocytes was seen in the posterior columns. No other abnormalities were seen.

Comment

The most remarkable attributes of this disease, from the pathologic point of view, are its localization and symmetric distribution in the base of the pons and its demyelinative character. These qualities were common to each of the three cases and deserve some elaboration, since their correct interpretation may enable us to understand the cause and mechanism of the disease.

In all three cases the lesion occupied the center of the basis pontis. In Cases 1 and 2 nearly all of the basis was involved, excepting a thin rim of tissue anteriorly and laterally. In these cases the lesion had extended for a short distance into the tegmentum, involving a few of the most medial fibers of the medial lemnisci. Vertically, the process extended from the lower border of the midbrain approximately to the level of the abducens nuclei and nerves in the lower pons. The lowest part of the pons, where it merges with the medulla, was not affected.

Within this focus nearly all the medullated sheaths were destroyed; not more than a few fine ones had survived, and in most places no intact sheaths could be seen. The myelin destruction thus involved all tracts regardless of their site of origin, termination, or probable function. These included the corticospinal, corticobulbar, and corticopontine tracts, as well as the pontocerebellar tracts and the infranuclear parts of the trigeminal nerves.

In contrast to the advanced degree of myelin destruction, the axis cylinders, nerve cells, and blood vessels were relatively well preserved. Only in the central cavitated focus were they affected to any significant degree. Elsewhere in the lesion, the exact histologic detail of the axis cylinders was difficult to evaluate because of their tendency to overstain wherever they were bare of myelin. They were thicker and more uneven in caliber than the fibers in the normal parts of the brain, and in some fascicles they appeared to have fused. There was no interruption in the integrity of most of these fibers. Only a few were broken into swollen, tortuous bits of argentophilic material, and bulbous swellings were seen at their fractured ends.

In general, the nerve cells of the basis pontis were well stained. In a few cellular aggregations, a slight numerical reduction was noted. Some of the remaining cells were of unusual appearance, being slightly larger, more rounded, and containing less chromatin than is normal for cells of the pontine nuclei. These changes are consistent with the cytoplasmic reaction that follows interruption of axis cylinders ("axonal reaction"). In view of the fact that some

fragmented axis cylinders were observed, this seems the most likely interpretation of this cellular change. Some of the nerve cells were shrunken and pyknotic with darkly stained nuclei, a cellular alteration which we interpreted as a postmortem artifact.

The blood vessels were patent in all parts of the lesion. The only alterations which they had undergone were a minor increase in cellularity in the walls of the venules, capillaries, and arterioles in the demyelinative part of the lesion and a slight adventitial fibrosis in the cavitating part of the lesion. These are best explained as reactions to the changes occurring in the surrounding tissues. There were no vascular, perivascular, or meningeal infiltrations of inflammatory cells.

Within the lesion there was a noteworthy lack of recognizable oligodendrocytes. Only in its margins could any of these cells be found, and here the nuclei were small and darkly stained, so that identification was difficult and uncertain. The microglial and adventitial histiocyte reactions, with the formation of macrophages, and the proliferation of fiber-forming astrocytes were in no way different from those which one is accustomed to see in any lesion in which there is extensive myelin destruction. No giant astrocytes or bizarre forms were noted. The degradation products of the myelin were present in the form of hematoxyphilic material (both as extracellular masses of fragmented myelin and as intracellular particles in the macrophages) and in the form of large, refractile, nonhematoxyphilic particles within macrophages. Thus, it would seem that the myelin breakdown proceeded in a manner characteristic of the usual lesions which involve the white matter of the brain and spinal cord.

It appeared that each lesion must have originated in the center of the pons, near the median raphe, and have spread centrifugally. The evidence favoring its central origin was that the oldest part of the lesion (cavitation) was found in the very center of the pons in Cases 1 and 2, and that the lesion was more or less limited to this region in Case 3. Its subsequent development was strikingly similar on the two sides of the pons, leading to a single large focus, the right and left halves of which were symmetric. The lesion appeared to develop by a marginal advance of this central focus in all directions, like a grass fire, and not from the confluence of multiple foci of myelin disintegration. One could observe large particles of degenerated myelin, not yet phagocytosed, in the advancing edge of the lesion. Here, in contrast to other parts, the tissue was loose and vacuolated, as though the disease process was in a more active phase. Furthermore, in Case 1 the largest macrophages containing hematoxyphilic granules were at the periphery; in Case 2 macrophages with these granules were found only at the periphery. These granules probably represented phagocytosed myelin fragments which had not yet been sufficiently degraded chemically to lose their hematoxyphilic staining property. These features are further evidence that the periphery of the lesion was the youngest part.

One can but speculate on the age of the lesions, since this feature could only be accurately judged by comparison with dated lesions of the same type, and we have had no previous examples of this disease. The date of onset of the symptoms does not necessarily mark the onset of the pathologic process, because it appears to have begun in the median raphe, a region from which one does not expect any symptomatic manifestations. If one draws a comparison with traumatic or ischemic lesions of different ages, one would suppose that the cavitating portion was at least six to eight weeks old. The tissue reactions in the more extensive demyelinated parts could have developed in two weeks in the first case and in four weeks in the second, periods which, in fact, did correspond to the duration of the pseudobulbar palsy and quadriplegia. The fact that some parts of the lesion are younger than others suggests that the disease pro-

gressed for several weeks and may have been progressing until the time of death.

The absence of Wallerian degeneration in the corticospinal tracts below the level of the lesion, or in the middle cerebellar peduncles or cerebellar hemispheres, probably has relatively little meaning. The survival period was at most four weeks, which would not allow sufficient time for the occurrence of secondary degeneration, as judged by myelin and cell stains.

The other neuropathologic changes were inconstant. In Case 1, the fresh hemorrhages in the pontine lesion and in the walls of the third and fourth ventricles were probably agonal and of no great significance. In the same case, and to a less extent in Case 3, there were a slight loss of medullated fibers and gliosis in the columns of Goll, indicating an abnormality of the posterior root fibers or sensory ganglion cells. In Case 3, lesions consistent with Wernicke's disease (superior hemorrhagic polioencephalitis), obviously of long standing, were found. In this case there was also swelling and chromatolysis of the anterior horn cells, indicating involvement of motor fibers, probably in the peripheral nerves. These changes are in keeping with the unmistakable clinical signs of polyneuropathy.

The differences which could be discerned among our three cases did not appear to be of fundamental significance. The most obvious difference, which has been described, was one of extent. The fact that the gliosis was greater in Case 2 than in Case 1 was surely due to the longer survival after the onset of the disease. Otherwise, the histologic changes were essentially the same in each case.

Clinical Manifestations and Clinical-Pathologic Correlation.—Although our experience is limited to only three cases, a general statement can be made regarding their clinical features and the relation of the clinical to the pathologic findings.

In all three cases there was a well-documented history of prolonged and serious alcoholism and of malnutrition of varying severity. The first patient was admitted to the hospital with pneumonia and delirium tremens. Both of these illnesses were resolving when, on the ninth hospital day, new neurologic signs developed. These evolved over a two-day period and resulted in death 13 days after their onset. The neurologic illness was characterized by flaccid quadriplegia, weakness of the face and tongue, and inability to speak and swallow. There was no response to painful stimuli; eventually the corneal reflexes were lost. All of these signs are readily explained by the lesion in the basis pontis. The flaccid quadriplegia was obviously related to the abrupt interruption of the corticospinal tracts. The Babinski signs and the reestablishment of reflexes in the limbs five days later could be explained by the dissipation of spinal shock. The weakness of the face and tongue and the disorder of speech and swallowing were probably pseudobulbar phenomena, resulting from the interruption of the corticobulbar tracts in the pons. The loss of corneal reflexes could be attributed to the involvement of the trigeminal nerve fibers; since these fibers were affected along the lateral margin, i. e., the youngest portion of the lesion, it is not surprising that they were lost relatively late in the illness. Clinically, one could not be certain that the lack of response to pinprick represented a loss of pain sensibility. It may have reflected only the depressed state of alertness and responsiveness. Indeed, there was no lesion in the spinothalamic pathways.

The second patient entered the hospital in a confused state, probably of alcoholic origin. After a period of initial improvement, another neurologic illness developed. The exact time of onset of this illness and its tempo of evolution cannot be stated precisely. It appeared on about the 11th hospital day and reached its maximum intensity 7 to 10 days later. It is not entirely clear from the clinical notes whether the legs were affected before the arms, but probably they were. Respiratory paralysis was responsible for the patient's death, on the 39th

hospital day. Again, the striking clinical features were the flaccid quadriplegia, the weakness of the tongue, and the inability to speak and swallow. In addition, there were other pseudobulbar phenomena, namely, emotional lability and forced crying. The pathologic findings in this case adequately explain these clinical features. The possibility of pontine paraplegia preceding the quadriplegia could be explained by the evolution of the lesion from a central focus, involving the medially situated leg fibers of the corticospinal tracts before the arm fibers. This patient's illness was of longer duration than that of the first case, and this fact is reflected in the older histologic appearance of the lesion.

Little can be said of the clinical features of the third case in relation to the pontine lesion. Neurologic symptoms and signs were present but could probably be attributed to a polyneuropathy. There were no clinical signs of involvement of the brain stem. This absence is entirely in keeping with the smallness of the lesion, which seemed to have spared the important pathways of the basis pontis.

The Cause and Mechanism.—In considering this aspect of the disease process, it is necessary first to determine whether or not the disease can be identified with well-recognized categories of disease of the nervous system.

The possibility of a vascular disease was entertained but was dismissed for several reasons. The large vessels at the base of the brain were patent in each case; there was no evidence of atherosclerosis or other arterial disease. The center of the pons is in an area that does not fall within the territory of any one branch of the basilar artery.[1,2] We have never observed a small central pontine infarct in occlusive disease of the basilar artery or its branches. We also considered the possibility of venous occlusion, but, again, there were no lesions of the veins. Finally, the nature of the lesion, with the escape of nerve cells and axis cylinders, was incompatible with a purely ischemic process.

Since demyelination was such a prominent feature in our cases, it is reasonable to consider the possibility that they represented a disease such as multiple sclerosis. This idea also appears to be untenable, mainly because of the nature of the lesion. Elsewhere one of us (R. D. A.) has presented a series of criteria for the pathologic diagnosis of multiple sclerosis, postinfectious encephalomyelitis, acute necrotizing hemorrhagic leukoencephalopathy, and Schilder's disease.[3] The perivenular localization of the myelin destruction and the prominence of adventitial infiltration of inflammatory cells, common to all diseases of this group, were lacking in our cases. Furthermore, a single, symmetrically disposed midline lesion of the pons could hardly be duplicated in any of these demyelinative diseases.

The possibility that this disease represents an unusual manifestation of Wernicke's superior hemorrhagic polioencephalitis occurred to us because of the obvious alcoholism and malnutrition of our patients and because of the occurrence of characteristic Wernicke lesions in Case 3. In our pathologic material, which includes more than 40 cases diagnosed as Wernicke's disease during life, the mammillary bodies were affected in a characteristic manner in every instance, and the walls of the third ventricle, periaqueductal region, and floor of the fourth ventricle, in the majority of cases.[4] Furthermore, histologically, the Wernicke lesion is characterized by destruction, in varying degree, of all parenchymal elements, not only of the myelin. A purely demyelinative focus of the pons was not found in any of our cases of Wernicke's disease, nor is such a lesion described in medical writings. It therefore seems justifiable to reject the idea that the pontine lesion is a variant of Wernicke's disease, and one must conclude that the Wernicke lesions in Case 3 were incidental.

Marchiafava-Bignami's disease was given even more careful consideration because of its symmetry and more or less demyelinative character. This disease is characterized by

a symmetric degeneration of myelin and, to a less extent, of axis cylinders, sometimes progressing to cavitation. The corpus callosum is most frequently affected, and less often the central parts of the anterior commissure, the central and convolutional cerebral white matter, the optic chiasm and radiations, and the middle cerebellar peduncles. The predilection of this disease for commissural fiber systems has been stressed, but this claim may not be completely justified, since it is not confined to these fibers. Inasmuch as these cases usually occur on a background of chronic alcoholism, a direct toxic effect has generally been accepted as the cause. In support of this idea, the work of Testa is frequently cited, in which lesions topographically similar to those of Marchiafava-Bignami's disease were reportedly produced in dogs by the chronic ingestion of alcohol.[5] However, the pathologic descriptions are far from satisfactory, and Testa's findings have not been confirmed by others. In the brains of cats which had been fed large amounts of alcohol for periods as long as two years we were unable to detect any abnormalities of this type, at least in sections strained by the methods of Nissl and Loyez.[6] On the other hand, there are frequent allusions to states of malnutrition in these patients. Furthermore, there are pathologically verified cases in which there was no history of alcoholism (King and Meehan[7]; Cases 9 and 11 of Gruner[8]). An additional point in favor of a nutritional etiology is the concurrence of Marchiafava-Bignami's disease and Wernicke's disease.[8-13]

From the histologic point of view the lesions in our cases bear a close resemblance to those of Marchiafava-Bignami's disease. In both the lesions are symmetric; there is relatively greater destruction of myelin than of other tissue elements, and no clear relationship of the lesions to blood vessels is evident; also inflammatory cells are not prominent. The analogy between the two processes cannot be carried further, however, because of the contrasting location of the lesions. In none of the reported cases of Marchiafava-Bignami's disease have pontine lesions been described, and none of our cases showed any change in the regions characteristically affected in Manchiafava-Bignami's disease. Furthermore, in our cases all fiber systems were indiscriminately affected, so that the disease could not be regarded as systematized.

Since the lesions in our cases do not conform to any of the familiar categories of nervous disease, one must analyze their own peculiar features. If a link could be established between these features and those of a recognized disease, it might provide a clue to the cause and mechanism. As has been stressed, the singular attributes of our cases are the demyelinative character and the specific localization and symmetric distribution in the basis pontis.

Insofar as demyelination is concerned, the curious manner in which whole segments of myelinated fibers become pale, then disintegrate, and finally, through the intermediation of macrophages, are converted into neutral fat, is analogous to the sequence of changes which follow regional ischemia of the brain. At the edge of the lesion there was the same extreme pallor of myelin sheaths that one sees after 12 to 24 hours or more of ischemia, and the same uneven swelling and vacuolation of the damaged fibers at the point of their junction with healthy parts of the fibers. The absence of vascular occlusion and the sparing of nerve cells admittedly exclude this factor of ischemia, although one may speculate that the disease represents the effect of impairment of oxidative processes or of the enzymes which subserve them.

Symmetry and constancy of localization must in themselves be meaningful attributes. Indeed, it may be said that diseases of the central nervous system of established etiology which possess these two qualities have an essential biochemical factor in their causation. That is to say, they are the result of the action of some exogenous or endogenous toxin or of a deficiency of some substance essential to the metabolism of nerve

tissue. Some examples which come immediately to mind are cyanide and carbon monoxide intoxication; anoxic, hypoglycemic, and hepatic encephalopathy; hepatolenticular degeneration, and diseases due to vitamin deprivation, such as Wernicke's disease and perhaps Marchiafava-Bignami's disease.

While we were considering the possibility of this disease being caused directly by the excessive ingestion of alcohol, this being the hypothetical toxin to which we have alluded, or by a secondary nutritional deficiency, an additional case came to our attention which may throw some light on the problem of etiology. This patient was not, and never had been, an alcoholic. Instead, the disease had developed on a background of severe malnutrition. Because of minor differences, which will emerge in the following account, it seemed advisable to separate this case from the first three cases.

Case 4.—A 53-year-old housewife died after an 18-month illness, characterized by anorexia, vomiting, intractable diarrhea, and severe weight loss. The significant findings on examination were weakness, depapillation and redness of the tongue, dryness and thinness of the skin, and an extreme degree of muscular wasting and cachexia.

General pathologic examination disclosed extreme emaciation and extensive changes in the skin and gastrointestinal tract, characteristic of scleroderma.

Neuropathologic Findings.—The brain, upper spinal cord, and sympathetic chain were examined after formalin fixation. The meninges were normal. The major blood vessels were free of atherosclerosis and patent throughout. Sections of the brain stem showed an area of softening in the midline of the basis pontis at the midpontine level. The lesion, shaped like an hour glass, measured approximately 1.5×0.7×1.0 cm. No lesions were noted elsewhere.

In sections stained for myelin, a discrete area of pallor occupied the middle of the basis pontis (Fig. 13). The lesion was roughly symmetric and biconcave in outline. The demarcation from normal tissue was not as sharp in this case as in the preceding ones. There was little encroachment upon the tegmentum, only the inferomesial borders of the medial lemnisci being involved. Within the body of the lesion, all the myelinated fibers had completely disappeared. Cavitation and tissue necrosis were more prominent in this case than in the others and not so strictly confined to the midportion of the lesion. In general, the nerve cells were well preserved within the area of demyelination, but in the midportion of the lesion some of them were lost, and many of the remaining ones were very pale (Fig. 14*A*). Most of the reacting cells were large, fat-filled macrophages. Several venules were surrounded by clusters of small macrophages (Fig. 14*B*). Fusiform fibrous astrocytes with large fibrils were present throughout the lesion, but they were much more numerous at the periphery, where they formed a dense isomorphic wall. There was a recent extravasation of blood around a large arteriole, unaccompanied by any cellular reaction or the presence of hemosiderin within macrophages. The blood vessels were patent and otherwise unremarkable. In contrast to the other cases, small collections of lymphocytes, partially encircling the vessels, were seen both within and outside the lesion (Fig. 14*A*).

Fig. 13 (Case 4).—Section through pons. The symmetric, centrally located focus of demyelination is evident. Loyez myelin stain.

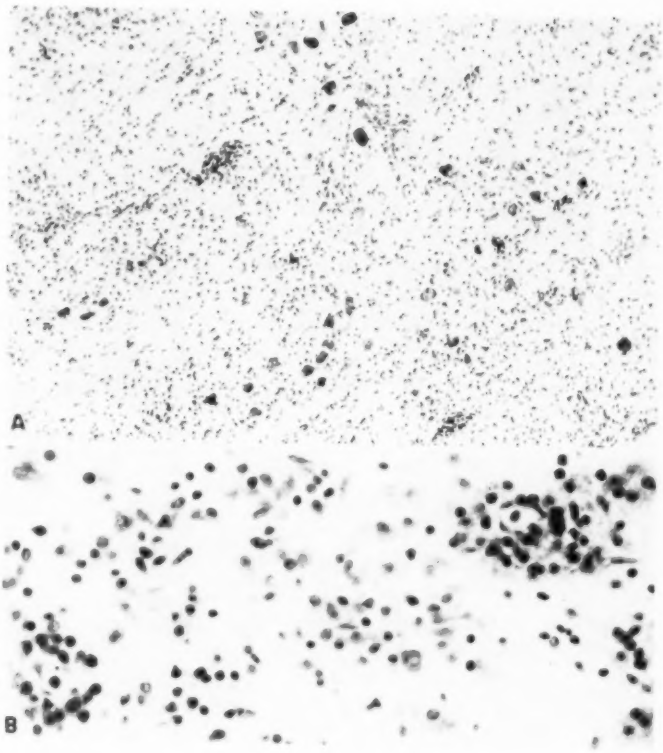

Fig. 14 (Case 4).—*A*, moderate loss of nerve cells within the lesion, and small perivascular collections of lymphocytes. Cresyl violet stain.

B, clusters of macrophages around blood vessels within the lesion. Cresyl violet stain.

No changes of a similar nature were seen in the remainder of the nervous system. In the *cerebral cortex* there were alterations in the nerve cells like those seen in pellagra. These changes were best seen in the large pyramidal cells and consisted of swelling, eccentricity of the nuclei, and central dissolution of the cytoplasmic chromatin. There was a slight increase in astrocytes throughout the cerebral cortex. No other significant changes were found elsewhere in the nervous system.

If this case is accepted as an example of the disease under discussion, the evidence for a nutritional etiology is greatly strengthened. Nevertheless, central pontine myelinolysis is clearly different from any of the recognized forms of nutritional deficiency of the central nervous system, i. e., Wernicke-Korsakoff syndrome, pellagra, subacute combined degeneration, and the experimental thiamine deficiency of animals. Furthermore, if nutritional deficiency is the important factor, it may not simply be a matter of vitamin deprivation, since in the first case parenteral vitamins were administered at least on one occasion just before the clinical signs of pontine disease developed.

Terminology.—Because of the unique clinical and pathologic features of the disease which we have described, we believe it should be given a special name. The term central pontine myelinolysis was chosen because it denotes both the specific anatomic localization of this disease and the remarkable unsystematic dissolution of medullated fibers. This description seems preferable to pontine demyelination, for two reasons. First, demyelination appears to represent only one phase in the evolution of this disease. In the central part of each lesion, what had begun as a demyelinative process eventually resulted in a destruction of all elements, even the supporting tissues, with resulting cavitation. Second, the term demyelination has been applied to such a diversity of diseases that it has come to lack precision. It usually connotes multiple sclerosis and

related disorders, and the points of difference between these diseases and our cases have already been stressed.

Summary

Attention is drawn to a singular pathologic entity encountered in four patients. It was localized in the rostral part of the pons and consisted of a single, sharply outlined focus of myelin destruction which indiscriminately affected all the fiber tracts. The axis cylinders and nerve cells were largely spared, and there were no inflammatory or vascular changes. The process probably began in the central portion of the pons and spread in a centrifugal manner, disposing itself symmetrically about the midline.

The condition under discussion is clearly differentiated from vascular diseases of the brain stem, Wernicke's disease, Marchiafava-Bignami's disease, and multiple sclerosis and related disorders. We have been unable to find any reference to a disease of this type in the medical literature of the past 75 years.

In two patients a dramatic clinical picture had developed, which could be attributed to the pontine lesion. Essentially this consisted of a rapidly evolving flaccid quadriplegia, with weakness of the face and tongue, and an inability to speak and swallow. In two other patients the lesion was probably too small to produce clinical signs.

The etiology is unknown. The nature and location of the disease favor either an exogenous or an endogenous intoxication, or a deficiency of some essential substance.

Reasons are given for designating this new disease as central pontine myelinolysis.

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REFERENCES

1. Foix, C., and Hillemand, P.: Contribution à l'étude des ramollissements protubérantiels, Rev. méd., Paris 43:287-305, 1926.

2. Kubik, C. S., and Adams, R. D.: Occlusion of the Basilar Artery—A Clinical and Pathological Study, Brain 69:73-121, 1946.

3. Adams, R. D., and Kubik, C. S.: Symposium on Multiple Sclerosis and Demyelinating Diseases: The Morbid Anatomy of the Demyelinative Diseases, Am. J. Med. 12:510-546, 1952.

4. Victor, M., and Adams, R. D.: Unpublished data.

5. Testa, U.: Lesioni del corpo calloso nell'alcoolismo subacuto sperimentale, Riv. sper. freniat. 52:559-574, 1928-1929.

6. Victor, M., and Adams, R. D.: Unpublished data.

7. King, L. S., and Meehan, M. C.: Primary Degeneration of the Corpus Callosum (Marchiafava's Disease), Arch. Neurol. & Psychiat. 36: 547-568, 1936.

8. Gruner, J. E.: Sur la pathologie des encéphalopathies alcooliques, Rev. neurol. 94:682-689, 1956.

9. Girard, P. F.; Garde, A., and Devic, M.: Considérations terminologiques, étiologiques, anatomiques et cliniques concernant l'encéphalopathie de Gayet-Wernicke, ses rapports avec le syndrome de Marchiafava-Bignami et la psychose de Korsakow, Rev. neurol. 88:236-248, 1953.

10. Garde, A.; Girard, P. F., and Pallasse, A.: L'Encéphalopathie hémorragique de Gayet-Wernicke et la dégénérescence subaiguë du corps calleux de Marchiafava-Bignami: A propos d'une observation anatomo-clinique, Rev. Lyon. méd. 1:99-108, 1952.

11. Schwob, R. A.; Gruner, J.; Foucquier, E.; Harl, J. M.; Françon, J., and Guerre, J.: Sur trois cas de syndrome confusionnel avec contracture chez des éthyliques: Le Problème des encéphalopathies carentielles, Rev. Neurol. 88:174-190, 1953.

12. Estrada, R., and Fuste, F.: Encefalopatia alcohólica: estudio de un caso en que se combinan los caracteres patológicos de la enfermedad de Marchiafava y los de la polioencefalitis de Wernicke, Arch. hosp. Univ., Habana 4:371-390, 1952.

13. Delay, J.; Boudin, G.; Brion, S., and Barbizet, J.: Étude anatomo-clinique de huit encéphalopathies alcooliques: encéphalopathie de Gayet-Wernicke et syndromes voisins, Rev. neurol. 94:596-601, 1956, Case 7.

Interaction in Simultaneous Motor Functions

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Introduction

Healthy persons are generally known to have a strong tendency toward symmetry of movements carried out simultaneously with the two upper extremities. Dissimilar movements, carried out simultaneously with the left and the right hand, entail a considerable effort, which is not always effective. This is a common observation in everyday life and in many tests used by psychologists or neurologists, for example, the motor test of Ozerecki.[1] It is a natural and common tendency to perform the same function with both hands. The phenomenon is of interest from the point of view of interaction of simultaneous kinesthetic stimuli from symmetrical extremities, and from that of reciprocal relations between them.

In neurological clinics, however, an additional problem is presented, namely, the kind of interaction between two motor functions performed by a person whose one hand is defective while the other one is healthy, whereby a motor action uniformly intended and planned is carried out differently by the two simultaneously operating extremities. In this instance, two simultaneous, but ultimately asymmetrical, actions are involved. Babinski,[2] in describing the phenomenon of diadochokinesia, has already called attention to changes in alternating movements in a healthy extremity cooperating with the paralyzed side.

Cohn[3] has more recently examined the interaction of bilaterally simultaneous functions in patients with unilateral paralysis, using alternating movements of pronation and supination of the hand as a test. The rhythm of movements carried out by his hemiplegic patients with the healthy hand was identical with that of movements performed by healthy control subjects, whereas the movements of the paretic hand were reduced in both rhythm and amplitude. Simultaneous bilateral movements interfered with both the rhymth and the amplitude of the movements of the healthy extremity, whereas improvement in the performance of the paretic hand was but slight or, most frequently, altogether absent. Cohn failed to note a similar phenomenon in peripheral pareses. Obviously, as is stated also by Cohn, the phenomenon discussed has nothing in common with synkinesia or mirror movements.

Cohn touched upon a number of very important problems in his paper. Our own investigations, involving a similar group of patients, occasioned an opportunity for a somewhat more detailed analysis of the phenomenon of interaction.

Materials and Methods

While testing kinesthetic disorders in 21 hemiplegic patients,[4] my colleagues and I examined also the phenomenon of interaction in simultaneous symmetrical movements of the two hands. The patients were asked to press a rubber bulb, at a rate most convenient for them, for a certain period of time (5, 10, 15, or 20 seconds). The pressures produced by the movements were transmitted by air to a writing point and recorded on a moving strip of paper. The patients examined carried out the movements with the healthy and with the paretic hand separately, and then with the two hands simultaneously. We deliberately chose the simple movement of pressing, unlike the alternating movement of pronation and supination of the hand in Cohn's experiments, since the problem of alternation of movements complicates, in our opinion, the drawing of conclusions by introducing an additional, unknown factor. Babinski established that impairment of alternation does not necessarily entail impairment of elementary movements, and that a simpler model of an elementary action was desirable. Analysis of a test in which the patient is

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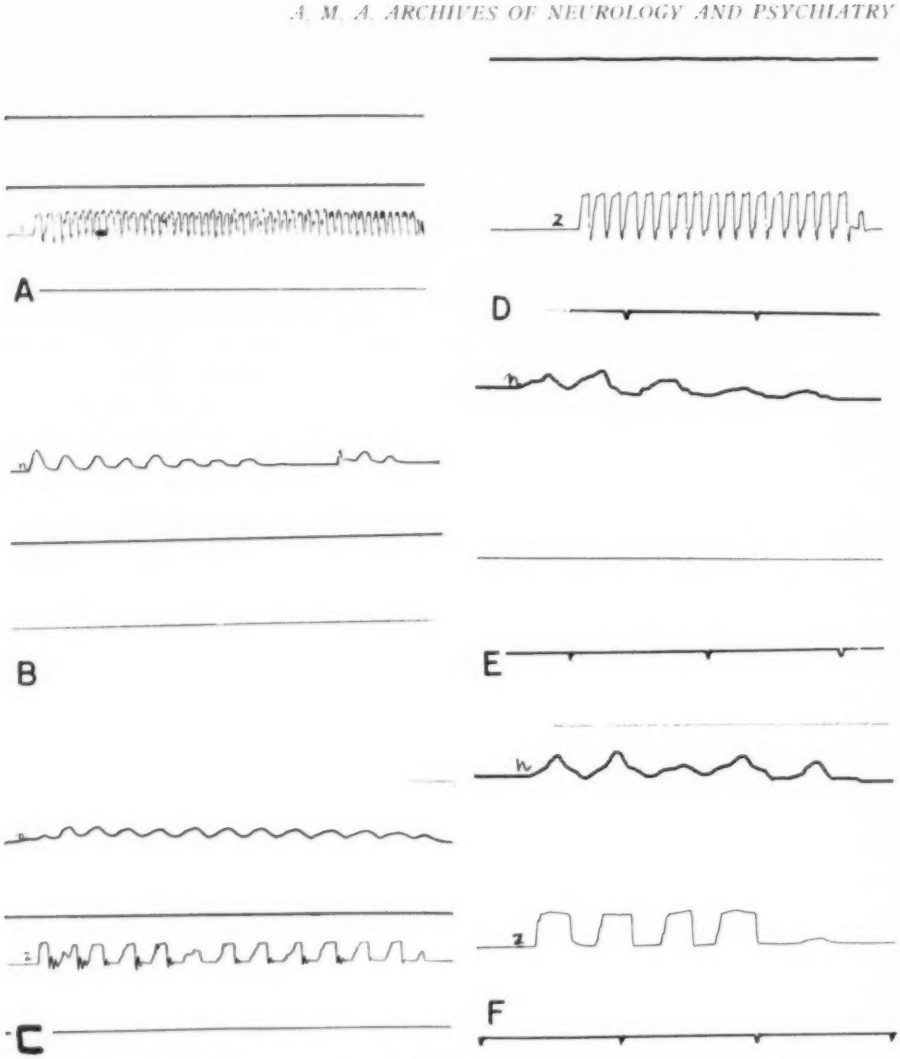

Fig. 1 (Case 1).—*A*, performance of the healthy hand alone; *B*, performance of the paralyzed hand alone; *C*, concurrent performance with the two hands. *D*, *E*, and *F*, performances of the healthy hand, the paralyzed hand, and the two hands together, one month after *A*, *B*, and *C* were recorded, when the paralyzed hand had gained in strength. Time interval, five seconds. Original size of record greatly reduced.

instructed to write simultaneously two different words with his left and with his right hand is undoubtedly also too complicated, and this applies also to numerous other tests.

In evaluating our recordings, we took into account the number of movements in five seconds and the total area (or surface) of the pen displacements (to take duration of individual contractions, as well as amplitude, into account), calculated by means of an analyzer of differential equations as the value of the integral of the function.* The apparatus directly calculates the graph of the function as the surface corresponding to the integral. In addition, we took into account also the amplitude of the action.

* Calculations by Mr. J. Wierzbowski. The analyzer is owned by the Institute of Mathematics, Polish Academy of Sciences.

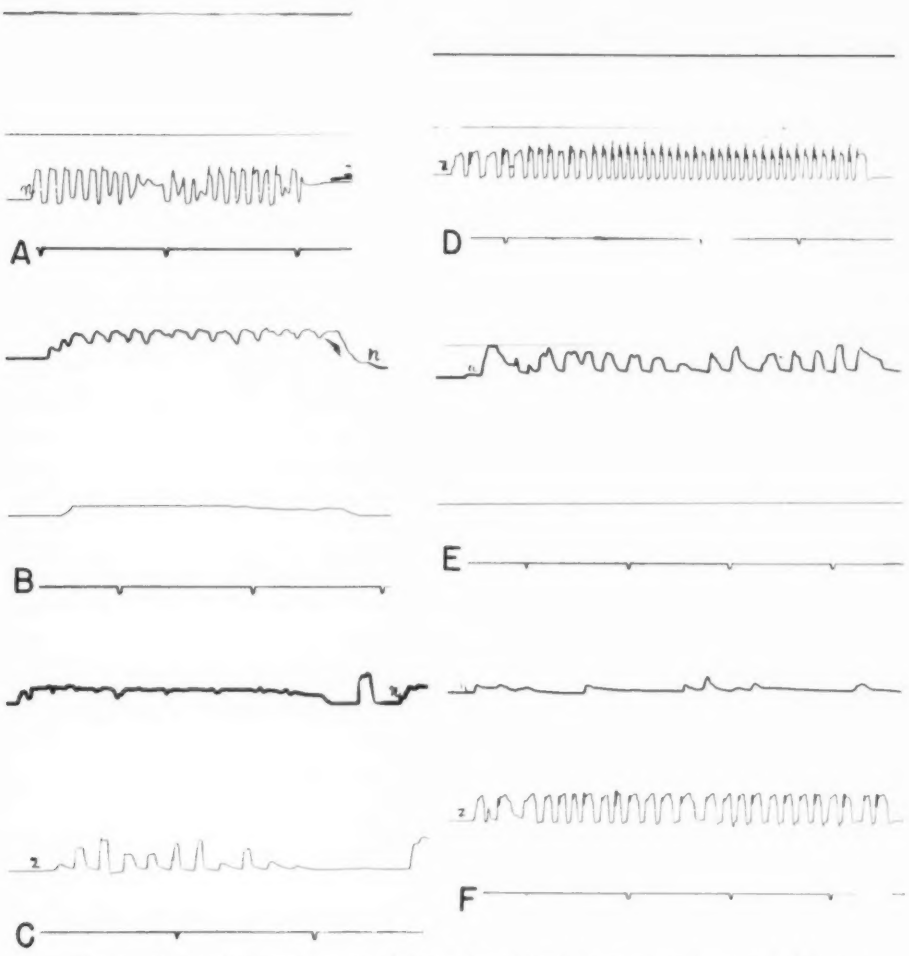

Fig. 2.—*A*, *B*, and *C*, performances of the unaffected hand, the paralyzed hand, and of the two concurrently in Case 2. *D*, *E*, and *F*, the same sequence in Case 3.

Results of Present Investigation

Simultaneous movements of both the paretic and the healthy hand had in all our patients a distinctly unfavorable effect on the performance of the latter. For example, in Case 1, with right hemiparesis due to thrombosis of the left middle cerebral artery, the intact left hand alone carried out the movements, at a rate of 13/5 sec. (Fig. 1*A*), an amplitude of 14 mm. and an area of 452 sq. mm. Movements of the paretic hand were as follows: rate 3/5 sec.; amplitude 12 mm.; total area 184 sq. mm. (Fig. 1*B*). When the two hands worked simultaneously, the movements of the paretic hand were improved but slightly: rate 3.2/5 sec.; amplitude 8 mm., i. e., even less than before, and total area 211.4 sq. mm. (Fig. 1*C*). Movements of the healthy hand were notably impaired under these conditions, rate and area being reduced to 3.25/sec. and 212.8 sq. mm. respectively (i. e., reduced almost to those of the paretic hand). The amplitude of the movement, however, remained almost unaltered, and was 13.5 mm. *D*, *E*, and *F* of Figure 1

record the similar performance of the same patient one month later, with improved strength in the hemiplegic hand.

Case 2, with left hemiparesis due to thrombosis of the right middle cerebral artery, showed in the healthy hand, working separately, a rate of 11/5 sec., an amplitude of 14 mm., and an area of 470 sq. mm. (Fig. 2*A*). The action of the healthy hand, working simultaneously with the paretic one, showed reduction of rate to 5/5 sec., of amplitude to 11 mm., and of area to 92.8 sq. mm., which is worse by 50% (Fig. 2*B*, *C*). The performance of the paretic hand was also less efficient than when the hands were working separately (unlike Cohn's test); the amplitude of the movements was reduced to 8 mm. (originally 11 mm.), and the area of the movement, to 312.8 sq. mm. (originally 478.4 sq. mm.). Thus, in this patient concurrent effort had an unfavorable effect on the healthy, as well as the paretic, hand.

Case 3, with left hemiparesis due to thrombosis of the right middle cerebral artery, showed even greater impairment of the performance of the affected hand. The performance of the right (healthy) hand, operating separately, showed a rate of 10.75/5 sec. (Fig. 2*D*), an amplitude of 18 mm., and an area of movement of 423.2 sq. mm.; the paralyzed hand, working separately, showed a rate of 4.25/5 sec., an amplitude of 12 mm. and an area of movement of 360 sq. mm. (Fig. 2*E*). When the hands operated jointly, the healthy hand worked at a rate of 6.25/sec., an amplitude of 15 mm., and an area of 285.2 sq. mm., whereas the performance of the paretic hand became notably worse; the rate was reduced to ±2.25 per second, and the movements were almost imperceptible (Fig. 2*F*) and irregular and had an area of 73.5 sq. mm.

We were next interested in the problem, not investigated by Cohn, whether the phenomenon depends in any way on the movement when the work of one hand becomes combined with that of the other. This problem has been frequently referred to in the literature regarding movements of healthy extremities, and it has been stressed that when movements of one hand are combined from the beginning with those of the other hand, the motor effects are reduced, as compared with those noted when the hand operates separately. However, movements of the other hand added at later time have been claimed to improve the performance of the first hand, depending on whether the original movements are started by the right or by the left hand (Tarasievich and Bulyghin[5] and Korobkov).[6]

In the first variant of our experiments, the movements were started by the healthy hand separately, and after 5, 10, or 15 seconds movements of the paretic hand were added.

The results of these experiments in Case 1 are shown in Figure 3. Movements of squeezing carried out by the healthy hand working separately had a rate of 8/5 sec., an amplitude of 8 mm., and an area of 533.6 sq. mm. After five seconds movements of the hemiplegic hand were added, and the bilateral movement had an unfavorable effect on the performance of the healthy limb: the rate was reduced to 3/5 sec., the amplitude to 7.5 mm., and the area to 458 sq. mm. (Fig. 3). As can be seen, the amplitude remained almost without change, whereas the rate was notably reduced. The rate of the movements of the paralyzed limb was 2.3/5 sec., the amplitude 8 mm., and the area 184 sq. mm. It is important to note two facts in the tracing: (1) Movements in the hemiplegic extremity ceased much sooner, although it was working together with the healthy one; (2) in spite of cessation of motor effects of the paralyzed hand (the last section of the graph), the rate of the movements carried out by the healthy hand failed to improve and did not return to the level recorded when it was working separately.

That the mere effort involved in an attempt to work with the paralyzed hand, even when futile as regards motor effects,

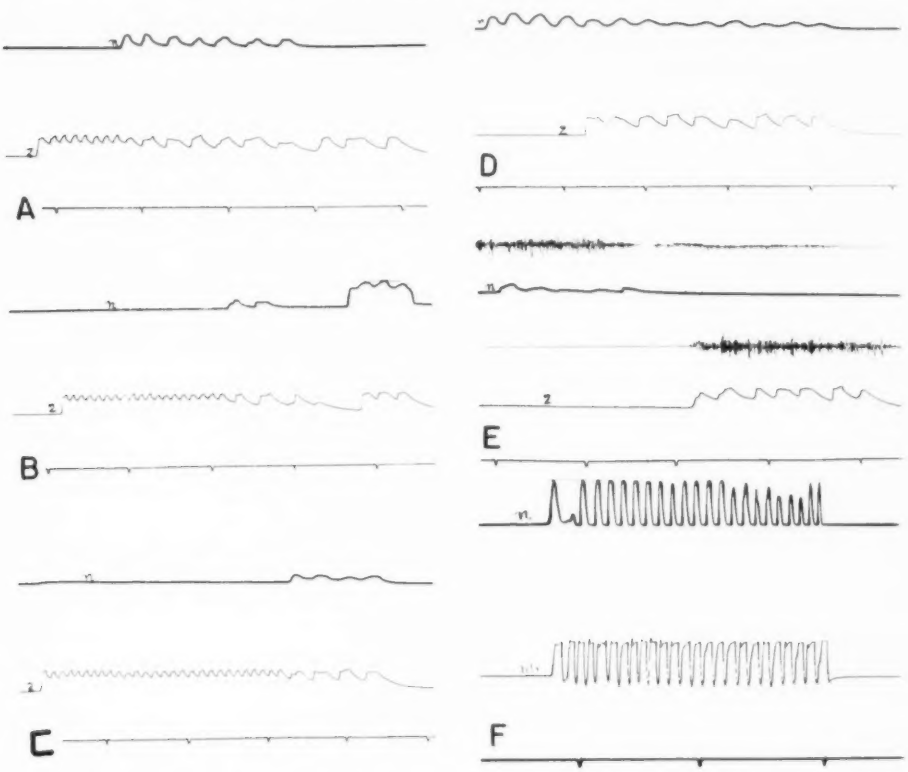

Fig. 3 (Case 1).—Movements of the paralyzed hand were added after the unaffected hand had been contracting for 5 seconds in *A* and for 10 seconds in *B*. In *C*, movements of the healthy hand were added after 5 seconds of contractions of the paralyzed hand and in *D*, after 10 seconds. In *E*, movements of the unaffected hand were added after 10 seconds, with action potentials of the flexor carpi of the paralyzed limb, above, and of the intact limb, below. No movements were perceptible in the paralyzed limb during the period of interaction. In *F*, passive movements at a similar rate were carried out in the affected hand, while the patient contracted the unaffected hand.

interferes in exactly the same fashion with the performance of the healthy limb as would actual movements indicates a central mechanism of the phenomenon of interaction.

When movements of the affected hand were added to those of the healthy limb after 10 seconds, the results were the same. In Figure 3 we see that the healthy hand worked separately at a rate of 9.5/5 sec., an amplitude of 13 mm., and an area of 579.6 sq. mm., and when movements of the hemiplegic hand were added, the functioning of the healthy one was changed very markedly: The movements became very irregular, like those of the affected limb; the rate was reduced to ±3.5/5 sec., the amplitude to 10.5 mm., and the area to 552 sq. mm. The movements of the hemiplegic hand were very irregular and distorted; the rate was 2.5/5 sec., and the area, 92 sq. mm.

Figure 3*C* illustrates another variant of this situation. The healthy hand worked separately for 15 seconds at a rate of 9.3 movements per second, an amplitude of 14 mm., and an area of 690 sq. mm. When movements of the affected limb were added, the rate of the healthy hand became depressed to 4/5 sec.; the amplitude remained

14 mm., and the area was reduced to 542.8 sq. mm. The frequency of the movements carried out by the hemiplegic hand was the same, but the amplitude was 5 mm. and the area 193.2 sq. mm.

It was evident that movements of the paralyzed hand have an unfavorable effect on those of the healthy hand, irrespective of when the former are added to the latter. This concerns, first and foremost, the rate of the movements, changes in amplitude being slight, or even altogether absent. This phenomenon was noted invariably in all the patients examined.

The situation was somewhat different in another variant of our experiments, namely, when movements were started by the hemiplegic hand and were afterward supplemented by those of the healthy extremity. This situation is exemplified in Figure 3*D*. Patient 1 carried out the ordered movements of pressing with the hemiplegic hand at a rate of 4/5 sec., and subsequently added movements of the healthy hand. The performance of the hemiplegic hand not only failed to improve; on the contrary, the rate of the movements became reduced to 3/5 sec., the amplitude dropped from 10 to 7 mm., and the area, from 349.6 to 276 sq. mm. The healthy hand, which worked at a rate of 9 movements in 5 seconds when tested separately, performed in this experiment 3 movements in 5 seconds.

This phenomenon became still more evident when the movements of the healthy hand were added to those of the paralyzed limb after 10 seconds (Fig. 3*E*). As can be seen from the graph, the movements carried out by the affected hand working separately were very irregular, being faintly discernible, and their area was a bare 128.6 sq. mm. When movements of the healthy hand were added, the movements of the affected hand ceased altogether. However, although there were no motor effects on the part of the hemiplegic limb, the healthy hand performed 3.5 movements in 5 seconds, instead of the normal 9 movements. This again confirms, in a manner analogous to Figure 3*A*, that the mechanism involved in this phenomenon is dependent on the innervation effort, and not on the motor effect manifested in the hemiplegic side. Another confirmation will be found in the electromyogram (Fig. 3*E*), which revealed impulses at a time when the hemiplegic limb appeared to be motionless.

An analogous picture was obtained when the hemiplegic hand worked separately for 15 seconds. The movements of the limb were very irregular, and the area was 92 sq. mm. When the movements of the healthy hand were added, those of the hemiplegic limb virtually ceased (area of the movements was 16 sq. mm.); however, irrespective of absence of motor effects on the paralyzed side, the healthy hand worked at a rate of 3 movements in 5 seconds, instead of at the normal rate of 9/5 sec.; the amplitude was as usual 14 mm., and the area was 239.4 sq. mm. Consequently, in this case, also, the performance of the healthy extremity was affected not by exhibited motor effects but by the innervation effort of the hemiplegic side. As can be seen, irrespective of the stage at which the movements of the healthy limb were added to those of the paralyzed hand, the effect was invariably alike: The healthy limb performed much worse; the rate became reduced, and even the amplitude was depressed. Unlike the healthy-paralyzed sequence, the movements of the hemiplegic hand were impaired, and occasionally even completely suppressed, as though "extinguished" by the functions of the healthy hand. Such intensity of effect was not found in experiments in which movements were started by the healthy hand and supplemented after a time by movements of the hemiplegic limb.

In order to test the role played by proprioceptive stimuli generated during passive movements, we carried out the procedure also used by Cohn. While the patient was working with his healthy hand, analogous passive movements were carried out in his

hemiplegic limb. As can be seen from Figure 3*F* (Case 1), passive movements had no effect on the performance of the healthy limb.

There remains another important problem, namely, whether improvement of the hemiplegic limb during rehabilitation is attended by a change in the relations between two interacting limbs. We have already referred to the performance of Patient 1 (Fig. 1). After one month of improving performance in the paralyzed limb, a second recording showed (Fig. 1*D*, *E*, *F*) that when the healthy hand worked separately, the frequency of the movements was 9/5 sec., the amplitude 15 mm., and the area 450 sq. mm. The hemiplegic hand carried out movements at a rate of 2.5/5 sec. and with an amplitude of 15 mm. (the area of the movements was 174.8 sq. mm.). When the hands worked together, the frequency of movements of the affected hand remained unchanged, i. e., 2.5/5 sec., but their amplitude increased to 10 mm. and their area to 202.4 sq. mm. Movements of the healthy hand, however, were seriously impaired; their rate dropped to 2.5/5 sec.; the amplitude was 14 mm., and the area, 358.8 sq. mm. Hence, improved performance of the paralyzed hand which, consequently, becomes capable of a greater effort, seems to interfere still more with the movements of the healthy hand, while its own action is only insignificantly enhanced by interaction.

Comment

As can be seen, the data obtained from the experiments confirm in general a familiar fact that performance of a healthy limb is adversely affected by simultaneous work of the symmetrical paralyzed limb. However, the nature of interaction suggests a new interpretation.

Cooperation with a hemiplegic limb appears to have an adverse effect, first and foremost, on the rate of the movements carried out by the healthy limb, while exerting little or no influence on the amplitude of the movements. This adverse effect becomes still more prominent at a later stage of improvement of motor functions, i. e., when the paralyzed limb begins to work more efficiently and becomes capable of a greater effort.

The negative effects of interaction concern also the hemiplegic limb, which frequently performs more slowly concurrently than when working alone, as though its movements were "extinguished" by the movements of the healthy limb. Occasionally even the amplitude of the movements is depressed (e. g., Fig. 2). At times during interaction the performance of the healthy hand becomes so much impaired that its movements become even slower than those of the hemiplegic limb (Figs. 3*A* and 1*C*).

Upon closer analysis of the phenomenon of interaction, we found that sequence of interaction was of importance. When the limbs do not start work together but the movements of one become switched into the rhythm of the other, it makes an essential difference whether the limb which started the original movements is the healthy or the hemiplegic one. When the patient started work with the paralyzed hand, addition of the movements of the healthy hand not only resulted in poor performance of that hand but also considerably impaired that of the paralyzed limb, leading occasionally to a complete cessation of the movements (Figs. 3*D*, *E*, *F*), as though involving a phenomenon of extinction. When, however, the movements are started by the healthy hand and movements of the hemiplegic hand are subsequently added, interaction usually results in impairment of the movements of the healthy limb. The time after which the movements of one limb are added to those of the other is altogether irrelevant.

The phenomenon described may be of practical significance in planning rehabilitation of hands in hemiplegic patients. In rehabilitation treatment, simultaneous symmetrical work of the two limbs is readily resorted to in order to improve the per-

formance of the hemiplegic limb. It appears, indeed, that movements are more easily revived in such conditions, but this involves a different mechanism. They do not become more efficient; on the contrary, they occasionally are even reduced as compared with those carried out by the hemiplegic limb separately. In this case there is interference of two phenomena: On the one hand, there is the adverse effect exerted by a pathological function on the collateral normal function, and, on the other hand, there is extinction of the functions of the weaker, disabled limb by the functions of the healthy one.

The mechanisms of the phenomenon discussed calls for elucidation. We agree with Cohn that the phenomenon does not involve synkinesia and that interaction has nothing in common with the latter, and in his assumption that the mechanism of interaction is central in nature. His thesis is further supported by our finding that, in spite of absence of motor effects on the hemiplegic side, when movements of the paralyzed limb ceased and the patient made merely futile efforts to bring the latter back into action, the movements on the healthy side were still notably impaired. On the other hand, we do not think it certain that the chief role is played in this phenomenon by the effector apparatus. Absence of any influence of passive movements of the hemiplegic hand on the functions of the healthy one does not seem to us to constitute an adequate argument. As is known, the current clinical methods of testing deep sensibility afford no insight into subtle kinesthetic disturbances, especially as regards perception of active movements, which differs from that of passive ones. It may be precisely the faulty supply of kinesthetic stimuli, released during active movements, which is the essential factor in the phenomenon of interaction in a healthy and a hemiplegic limb. There is interference between abnormal and normal afferent function, an effect of the former on the latter. This afferent function, of course, is elicited not only by pathological movements but also by the effort involved in attempting to carry out the movement.

We therefore believe the phenomenon of interaction to correspond to the phenomenon of interference of two rival stimuli (e. g., visual, auditory, cutaneous, etc.)[7-11] known in every field of perception and taking place in the central portions of the analyzer (i. e., in the receptor apparatus in the broadest sense of the word). Observation reveals in the phenomenon the same properties of "extinction" as in the perception of other two simultaneous stimuli.

Summary

The results of investigations into motor interaction in a healthy and in a paralyzed limb in 21 hemiparetic patients are discussed.

In agreement with data obtained by other authors, I found movements of the healthy limb to be impaired by interaction with the hemiplegic extremity. The impairment concerned especially the rate of the movements, and to a less degree, if at all, their amplitude. Contrary to data found in the literature, interaction had also an adverse effect on the performance of the healthy hand.

Manifestations of interaction differed, depending on whether movements were started with the healthy hand and movements of the paralyzed hand were added after a time, or the reverse. From the facts revealed in the course of experiments, conclusions that may be of value in rehabilitation are drawn. A tentative explanation of interaction between a paralyzed and a healthy limb is presented in terms of interference of normal and distorted kinesthetic perception, resembling other types of "extinction."

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REFERENCES

1. Ozerecki, N.: Methodik der kollektiven Prüfung der Motorik bei Kindern, Ztschr. Kinderforsch. 35:332, 1929.

2. Babinski, J.: Sur le rôle du cervelet dans les actes volitionnels nécessitant une succession rapide des mouvements (diadococinésie), Rev. neurol. 10: 1013, 1902.

3. Cohn, R.: Interaction in Bilaterally Simultaneous Voluntary Motor Function, A. M. A. Arch. Neurol. & Psychiat. 65:472, 1951.

4. Hausmanowa-Petrusewicz, I.: Disorder of Kinesthetic Sensation in Hemiplegia, Postepy neurol. neurochir. psychiat. 3:241, 1957.

5. Tarasievich, A., and Bulyghin, I.: Physiology of Motor Analyzer in Man, Fiziol. biokhem. farmak., p. 597, 1955.

6. Korobkov, A. V.: Modifications of Maximum Rate of Finger Movements Under Influence of Movements of the Opposite Extremity, Fiziol. zhur. 41:43, 1955. (Russian.)

7. Bender, M. B.: Extinction and Precipitation of Cutaneous Sensations, Arch. Neurol. & Psychiat. 54:1, 1945.

8. Bender, M. B., and Tauber, H. L.: Phenomena of Fluctuation, Extinction and Completion in Visual Perception, Arch. Neurol. & Psychiat. 55:627, 1946.

9. Furmanski, A.: The Phenomena of Sensory Suppression, Arch. Neurol. & Psychiat. 63:205, 1950.

10. Denny-Brown, D.; Meyer, J. S., and Horenstein, S.: Significance of Perceptual Rivalry Resulting from Parietal Lesion, Brain 75:433, 1952.

11. Cohn, R.: The Babinski Sign, J. Neurophysiol. 11:193, 1948.

Extraocular Motor Disturbances in Primary Brain Tumors

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The incidence of disorders of involvement of the third, sixth, and fourth cranial nerves in a group of 235 primary brain tumor cases, verified by autopsy, admitted to the Philadelphia General Hospital over a 20-year period was studied. No cases of metastatic tumors, tumors by extension, granulomas, vascular malformations, or subclinical tumors, and no cases admitted within 12 hours of death were included in this survey. There were 157 gliomas, of which over 50% were glioblastoma multiforme. The remaining, nongliogenous group comprised 78 tumors, of which over 60% were meningiomas.

Sixty cases showed extraocular motor involvement, most frequently encountered (50% of cases) as unilateral isolated third nerve palsy. Abducens involvement was half as frequent and was also usually unilateral and isolated. No instance of isolated trochlear palsy was reported. Combinations of extraocular motor nerve involvement, more frequently bilateral, occurred in 20% of cases.

The brain tumor cases were divided into groups based on type and location of the lesion. Cases in which location was imprecise or there was coexistence of other pathology were eliminated, leaving the cases which are analyzed in Table 1.

It is noted that intramedullary tumors occupying the region of the extraocular nerve nuclei in the tectum and tegmentum differ from tumors of most other areas (excepting base and angle groups) in that they are most apt to cause extraocular palsies. χ^2-evaluation showed a significant difference ($P = 0.05$-0.02) from hemispheric lesions. Nongliogenous tumors at the base and about the chiasm and sella, and also those in the cerebellopontine angle also showed a relatively high incidence of disorders of the extraocular apparatus. The meningiomas of the convexities showed the lowest percentage of occurrence of extraocular muscle disorders.

TABLE 1.—*Analysis of Brain Tumors by Site and Type*

	No. Total	No. EOM *	% EOM
A. Gliomas (131)			
1. Centrum ovale (fronto-parietal)	38	8	21.1
2. Temporal	45	12	26.6
3. Basal ganglia	36	10	27.8
4. Basal ganglia and brain stem	8	7	87.5
5. Brain stem	4	3	75.0
B. Nongliomas (51)			
1. Convexity	21	3	14.3
2. Base (sellar)	20	7	35.0
3. Angle (cerebellopontine)	10	4	40.0
C. Indirect (A1, B1)	59	11	18.6
D. Direct (A4, A5)	12	10	83.3

* EOM = extraocular motor involvement.

Patients evidencing extraocular disorders were considered from the standpoint of the specific type of cranial nerve (extraocular) involvement. In Table 2 the instances of isolated third and sixth nerve involvement are indicated as they occurred in each of the eight groups and in groups of tumors remote from the oculomotor system (C), as well as in those tumors involving the region of the extraocular nerve nuclei (D). The lateralization is designated.

Within the groups of supratentorial gliomas, the incidence of extraocular disorders represented 10% to 15% of the total

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TABLE 2.—*Extraocular Motor Disturbances and Types of Third and Sixth Nerve Involvement* *

	No. III	% III	U	C	I	?	B	No. VI	% (Total) VI	U	C	I	?	B
A. Gliomas														
1. Centrum ovale	5	13.2	5	2	3	0	0	3	7.9	3	1	1	1	0
2. Temporal	7	15.5	4	2	2	0	3	2	4.4	1	1	0	0	0
3. Basal ganglia	4	11.1	2	1	1	0	2	5	13.9	2	1	0	1	3
4. Basal ganglia, brain stem	4	50.0	2	1	1	0	2	0	0.0	0				0
5. Brain stem	1	25.0	0				1	2	50.0	2	0	0	2	0
B. Nongliomas														
1. Convexity	2	9.5	2	2	0	0	0	1	4.7	1	1	0	0	0
2. Base	4	20.0	3	0	2	1	1	0	0.0	0				0
3. Angle	2	20.0	1	1	0	0	1	1	10.0	1	0	0	1	0
C. Indirect (A1, B1)	7	11.8	7	4	3	0	0	4	6.7	4	2	1	1	0
D. Direct (A4, A5)	5	41.6	2	1	1	0	3	2	16.6	2	0	0	2	0

* U indicates unilateral; C, contralateral; and B, bilateral i, ipsilateral; ?, side unknown.

number of cases and was approximately equal in the three groups. Tumors of the basal ganglia showed the lowest incidence of isolated oculomotor disorder. Unilateral involvement occurred twice as frequently as did bilateral, and contra- and ipsilateral involvement were of about equal frequency.

Extraocular motor involvement of the third nerve was slightly commoner in sellar and angle tumors than in the preceding groups mentioned.

The lowest incidence of third nerve palsy occurred in extramedullary tumors of the convexities.

Exclusively unilateral involvement occurred in the group of tumors having no direct relationship to the oculomotor system (C), and no laterality was evident. In lesions involving the oculomotor centers, bilateral involvement was characteristic.

Intramedullary tumors of the tectum and tegmentum showed the highest frequency of isolated abducens palsy, and this was otherwise negligible. Unilateral involvement was commoner in cases of sixth nerve palsy, except for groups of basal ganglia tumors.

Consideration of the groups from the standpoint of multiple involvement discloses that multiple nerve involvement occurred only in cases in which the lesion was in close relation to the extraocular motor apparatus. One-quarter of the cases of cerebellopontine angle and half of those in the sellar region having extraocular motility involvement showed combined nerve disorders, usually abducens and oculomotor.

A comparison of the type of nerve involvement in the various groups is presented in Table 3.

Isolated third nerve palsy was twice as common as was sixth nerve palsy in cases of

TABLE 3.—*Extraocular Motor Disturbances in Third and Sixth Nerve Involvement*

	No. EOM	No. III	% (EOM) III	No. VI	% (EOM) VI	No. Comb.	% (EOM) Comb.
A. Gliomas							
1. Centrum ovale	8	5	62.5	3	37.5	0	0.0
2. Temporal	12	7	58.3	2	16.6	3	25.1
3. Basal ganglia	10	4	40.0	5	50.0	1	10.0
4. Basal ganglia, brain stem	7	4	57.1	0	0.0	3	42.9
5. Brain stem	3	1	33.3	2	66.6	0	0.0
Total	40	21	52.5	12	30.0	7	17.5
B. Nongliomas							
1. Convexity	3	2	66.6	1	33.3	0	0.0
2. Base	7	4	57.1	0	0.0	3	42.9
3. Angle	4	2	50.0	1	25.0	1	25.0
Total	14	8	57.1	2	14.3	4	28.6
C. Indirect (A1, B1)	11	7	63.6	4	36.4	0	0.0
D. Direct	10	5	50.0	2	20.0	3	30.0

hemispheric tumors. Tumors of the temporal lobe, sella, and chiasm exhibited a greater incidence of third nerve as well as multiple nerve involvement. Basal ganglia gliomas showed approximately equal incidences of isolated oculomotor and abducens palsy. A consideration of lateralization in the various groups reveals that no predominance of laterality relative to tumor site is evidenced. Unilateral and bilateral involvement were of approximately equal incidences in temporal lobe tumors and in basal ganglia gliomas, whereas bilateral extraocular muscle involvement was absent in hemispheric tumors. In both hemispheric and temporal lobe tumors increased intracranial pressure was encountered in a larger number of patients with extraocular motor involvement (83% and 75% respectively) than in those without such involvement (40% and 9% respectively). This is significant at the 0.01 level of confidence (using χ^2).

Comment

A review of the literature discloses relatively little treatment of extraocular motility problems as encountered in surveys of large series of brain tumors.[4,33,34,36,38] Table 4 lists a collection of brain tumor series, comprising 1132 cases. Extraocular disturbances were mentioned as occurring in 276 cases, or 24.4%, of the series. This correlates closely with the findings in the present series.

The over-all incidence of various types of extraocular motor disturbances will be noted in Table 5, where it is seen that isolated abducens nerve palsy constituted the most frequent manifestation, followed closely by third nerve involvement. This finding is the reverse of the relatively high over-all incidence of third nerve involvement noted in the present survey.

The data available, though scarce, showed predominance of unilateral involvement, especially abducens palsies, where very little difference in the side of involvement is noted.

TABLE 4.—*Extraocular Motor Disturbances in Brain Tumor Series*

Over-All Groups	Total No.	EOM No.	EOM %
Torkildsen[33]	356	132	37.1
Cushing and Eisenhardt[7]	256	26	10.2
Globus and Silverstone[11]	171	45	26.3
Collier[8]	161	14	8.7
Dowman and Smith[9]	100	34	34.0
Schwarz and Rosner[10]	64	17	26.5
Cushing[6]	24	8	33.3
	1132	276	24.4
Parsons	235	60	25.5

TABLE 5.—*Extraocular Motor Disturbances in Various Series*

	EOM No.	III No.	III % Total	III % EOM	VI No.	VI % Total	VI % EOM	C No.	C % Total	C % EOM
Globus and Silverstone [14]	45	10	5.8	22.2	26	15.0	57.8	9	5.5	20.0
Cushing and Eisenhardt [7]	26	11	4.3	42.3	9	3.5	34.6	6	2.4	23.1
Schwarz and Rosner [16,40]	17	17	26.5	100.0	0	0.0	0.0	0	0.0	0.0
Collier [9]	14	2	1.3	14.3	12	7.4	85.7	0	0.0	0.0
Cushing [5]	8	3	12.5	37.5	3	12.5	37.5	2	8.3	25.0
	110	43	6.4	39.1	50	7.8	45.5	17	2.5	15.5
Parsons	54	29	15.9	53.7	14	7.7	25.9	11	6.0	20.4

TABLE 6.—*Extraocular Motor Disturbances with Frontoparietal Tumors in Various Series*

	Total No.	EOM No.	EOM %	III No.	III % EOM	VI No.	VI % EOM	C No.	C % Total EOM
Globus and Silverstone [14]	57	14	24.5	1		11		2	
Kolodny [10]	30	9	30.0	6		3		0	
Dowman and Smith [9]	28	10	33.3	0		10		0	
Diez [8]	10	3	30.0	2		2		0	
Cushing [5]	5	1	20.0	1		0		0	
Cushing and Eisenhardt [7]	234	42	17.9	14		27		2	
	364	79	21.7	24	30.4	53	67.1	4	5.1
Parsons	59	11	18.6	7	63.6	4	36.3	0	0.0

Only about 15%-20% of hemispheric and convexity tumor cases in the literature exhibit impairment of extraocular motor functions, and this figure is closely correlated with results of the current study. Table 6 compares cases of tumors of this area from the literature with tumors of the present study with respect to extraocular motor palsy. In contrast to this series, preponderance of sixth nerve involvement is observed.

Bilateral involvement (either third or sixth nerve) was more frequent (40%-45%) than was the case with the present series.

Table 7 reveals results of studies of temporal lobe tumors wherein mention of extraocular motor disturbances is made.

Ocular motor palsies are more frequent than in the case of hemispheric lesions, and oculomotor involvement (especially homolateral) predominates, as was demonstrated by the present study.

A selected group of studies of basal ganglia tumors [5,12] exhibited a low incidence of extraocular motor involvement, about equally divided between sixth and third nerve implication (as was seen in the current study).

TABLE 7.—*Extraocular Motor Disturbances with Temporal Lobe Tumors*

	Total No.	EOM No.	EOM %	III No.	III % EOM	VI No.	VI % EOM	C No.	C % EOM
Sanford and Bair [37]	31	25	11.8	9	36.0	16	64.0	0	0.0
Globus and Silverstone [14]	58	23	39.7	7	30.4	12	52.2	4	17.4
Rowe [34]	52	12	23.0	12	100.0	0	0.0	0	0.0
Cushing and Eisenhardt [7]	38	21	55.2	21	100.0	0	0.0	0	0.0
Kolodny [10]	39	10	25.6	4	40.0	4	40.0	2	20.0
Schlesinger [35]	11	2	18.1	1	50.0	1	50.0	0	0.0
Ganner and Stiefler [11]	6	1	16.7	1	100.0	0	0.0	0	0.0
	235	94	40.0	55	58.5	33	35.1	6	6.4
Parsons	45	12	26.6	7	58.3	2	16.6	3	25.1

The present study disclosed the highest incidence of extraocular motor disorders in brain stem tumors, where bilaterality and combined nerve involvement constituted distinguishing features. The small series of 54 cases culled from the literature [1,10,23] confirms these findings. Fifty per cent of the cases showed extraocular motor implication, equally divided between single and combined nerve involvement. The specific type of involvement (oculomotor, abducens, etc.) is dependent upon the portion of the brain stem primarily affected.

The mechanisms for the involvement of ocular motor nerves by intracranial tumors include interference with blood supply, direct impingement by the tumor upon the ocular motor apparatus (nuclei or fibers), and pressure effects, which may be either local or distant. Certain instances of ocular motor nerve palsy are unaccounted for by these mechanisms.

A high incidence of ocular muscle palsy is to be anticipated in lesions directly impinging upon the oculomotor apparatus; pressure effects are less obvious. The statement is made that the long intracranial course of the abducens nerve along the inferior surface of the pons renders it readily compressed between the latter and branches of the basilar artery by anything which increases intracranial tension with pontine displacement.[2] This is the basis for the familiar false localizing sign of isolated sixth nerve paralysis in lesions associated with increased intracranial pressure. Third nerve involvement is less frequently stressed in this connection.[13] It is noted that the oculomotor nerve emerges from the midbrain in the interpeduncular fossa at a sharp angle formed by the peduncle and the pons, at which point it passes through the crotch of the fork made by the posterior cerebral and superior cerebellar arteries as they are given off the basilar artery. Approximately 2 cm. from its emergence it penetrates arachnoid and dura to enter the cavernous sinus.[19,22] In the presence of brain-stem shifts due to generalized increased intracranial pressure, the third nerve is vulnerable both to strangulation between the two terminal branches of the basilar artery and to traction at the point of dural exit. These mechanisms may account for the significant incidence of third nerve palsies encountered in this group of tumors distant from the ocular motor apparatus (hemispheric lesions).

The consideration of local pressure effects is relevant to the higher incidence of third nerve palsy seen in temporal lobe tumors.[13] The pathogenesis of oculomotor palsy accompanying temporal lobe tumors may be that of compression of the oculomotor nerve by the uncus, which has herniated through the incisura of the tentorium.[2,13,31]

Conclusions

Extraocular motor disturbances are encountered in approximately one-quarter of all cases of primary brain tumors, in accordance with findings of previous studies.

Oculomotor nerve palsies are almost twice as common as are abducens nerve palsies, in contrast with what has previously been mentioned.

The type of extraocular motor involvement is related to the location rather than to the type of tumor.

In tumors distant from the extraocular motor system (hemispheres and convexities), several characteristics of extraocular palsies have been noted.

(*a*) Involvement is unilateral and affects either side with equal frequency. Reports from the literature indicate a higher percentage of bilateral, as well as a preponderance of ipsilateral, involvement.

(*b*) Third nerve involvement is twice that of the sixth and just the reverse of what is derived from analysis of the literature.

(*c*) Multiple nerve involvement is not encountered, consistent with previous reports.

(*d*) Increased intracranial pressure was significantly greater in tumors having extraocular nerve involvement.

In temporal lobe tumors a slightly different characteristic of extraoculomotor involvement has been demonstrated in that

third nerve involvement is three times that of sixth nerve involvement; less difference in incidence is noted in the literature.

In tumors implicating the brain stem, either directly or by extension from above downward, or by displacement from without the neuraxis (basilar and angle lesions), certain observations may be made.

(*a*) The character of involvement (third, fourth, or sixth, or combined ocular motor nerves) depends upon the portion of the brain stem affected.

(*b*) A high incidence of bilateral and combined nerve involvement is noted.

Summary

1. An analysis of signs of impairment of extraocular motility in a series of patients with primary brain tumors is made. A comparison with analysis of the extraocular motor nerve signs reported in large series of similar tumors in the literature is made and mechanisms discussed.

2. The results of this survey suggest that extraocular motor disturbances constitute a frequent and important sign of brain tumor, being exceeded only by pyramidal symptoms, signs of increased intracranial pressure, convulsions, pupillary changes, and mental alterations, including depression of consciousness.

3. The importance of oculomotor nerve palsies in tumors distant from the extraocular motor system is as great as that of abducens nerve involvement. Unilateral involvement of either nerve suggests the presence of a hemispheric lesion; unilateral oculomotor palsy is especially characteristic of temporal lobe lesions.

4. Bilateral or multiple extraocular motor nerve signs suggest basilar or brain stem lesions.

5. The presence of extraocular motor nerve involvement suggested increased intracranial pressure in temporal and hemispheric tumors.

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REFERENCES

1. Alpers, B. J., and Watts, J. W.: Mesencephalic Glioma: A Clinical and Pathologic Analysis of 10 Cases, Arch. Neurol. & Psychiat. 34:1250-1273 (Dec.) 1935.

2. Bailey, P.: Intracranial Tumors, Ed. 2, Oxford, England, Blackwell Scientific Publications, 1947.

3. Collier, J.: The False Localising Signs of Intracranial Tumour, Brain 27:490-508, 1904.

4. Cushing, H.: Intracranial Tumours: Notes upon a Series of 2000 Verified Cases with Surgical-Mortality Percentages Pertaining Thereto, Springfield, Ill., Charles C Thomas, Publisher, 1932.

5. Cushing, H.: Strangulation of Nervi Abducentes by Lateral Branches of the Basilar Artery in Cases of Brain Tumour, Brain 33:204-235 (June) 1910.

6. Cushing, H.: Tumors of the Nervus Acusticus and Syndrome of the Cerebellopontile Angle, Philadelphia, W. B. Saunders Company, 1917.

7. Cushing, H., and Eisenhardt, L.: Meningiomas: Their Classification, Regional Behaviour, Life History, and Surgical End Results, Springfield, Ill., Charles C Thomas, Publisher, 1938.

8. Diez, M. A.: Ophthalmologic Syndromes Associated with Tumors of the Frontal Lobe, Rev. Asoc. méd. argent. 60:194-200 (April) 1946.

9. Dowman, C. E., and Smith, W. A.: Intracranial Tumors: A Review of 100 Verified Cases, Tr. South. S. A. 40:308-359, 1927.

10. Foerster, O., and Gagel, O.: Die encephalen Tumoren der Oblongata, Pons und des Mesencephalons, Ztschr. ges. Neurol. u. Psychiat. 168: 295-331, 1940.

11. Ganner, H., and Stiefler, G.: Zur Symptomatologie der Schlafclappentumoren Arch. Psychiat. 101:399-451, 1933.

12. Globus, J. H., and Silverstone, S. M.: Diagnostic Value of Defects in Visual Fields and Other Ocular Disturbances, Associated with Supratentorial Tumors of the Brain, Arch. Ophth. 14: 325-380 (Sept.) 1935.

13. Haymaker, W.: Bing's Focal Diagnosis in Neurological Diseases, St. Louis, C. V. Mosby Company, 1956.

14. Jefferson, G.: The Tentorial Pressure Cone, Arch. Neurol. & Psychiat. 40:857-876 (Nov.) 1938.

15. Jefferson, G.: Extrasellar Extensions of Pituitary Adenomas, President's Address, Proc. Roy. Soc. Med. 33:433-458 (May) 1940.

16. Kennedy, F.: Symptomatology of Temporosphenoidal Tumors, Arch. Int. Med. 8:317-350 (Sept.) 1911.

17. Kernohan, J. W., and Woltman, H. W.: Incisura of the Crus Due to Contralateral Brain Tumor, Arch. Neurol. & Psychiat. 21:274-287 (Feb.) 1929.

18. Kessler, E.: Über Häufigkeit, Aetiologie und Prognose der Augenmuskellähmungen, Confinia neurol. 4:159-170, 1942.

19. Kestenbaum, A.: Clinical Methods of Neuro-Ophthalmologic Examination, New York, Grune & Stratton, Inc., 1946.

20. Kolodny, A.: Symptomatology of Tumor of the Frontal Lobe, Arch. Neurol. & Psychiat. 21: 1107-1127 (May) 1929.

21. Kolodny, A.: Symptomatology of Tumours of the Temporal Lobe, Brain 51:385-417 (Oct.) 1928.

22. Lyle, D. J.: Neuro-Ophthalmology, Springfield, Ill., Charles C Thomas, Publisher, 1945.

23. Foerster, O.; Gagel, O., and Mahoney, W.: Die encephalen Tumoren des verlängerten Markes, der Brücke und des Mittelhirns, Arch. Psychiat. 110:1-74, 1939.

24. Meyer, A.: Herniation of the Brain, Arch. Neurol. & Psychiat. 4:387-400 (Oct.) 1920.

25. Moersch, F. P.; Craig, W. McK., and Kernohan, J. W.: Tumors of the Brain in Aged Persons, Arch. Neurol. & Psychiat 45:235-245 (Feb.) 1941.

26. Rowe, S. N.: Verified Tumor of Temporal Lobe: Critical Review of 52 Cases, Arch. Neurol. & Psychiat. 30:824-842 (Oct.) 1933.

27. Sanford, H. S., and Bair, H. L.: Visual Disturbances Associated with Tumors of the Temporal Lobe, Arch. Neurol. & Psychiat. 42:21-43 (July) 1939.

28. Schlesinger, B.: Syndrome of Fibrillary Astrocytomas of the Temporal Lobe, Arch. Neurol. & Psychiat. 29:843-854 (April) 1933.

29. Schwarz, G. A., and Rosner, A. A.: Clinicopathologic Consideration of Displacement and Herniation of Hippocampal Gyrus Through Incisura Tentorii, Arch. Neurol. & Psychiat. 43:1040-1044 (May) 1940.

30. Schwarz, G. A., and Rosner, A. A.: Displacement and Herniation of Hippocampal Gyrus Through Incisura Tentorii, Arch. Neurol. & Psychiat. 46:297-321 (Aug.) 1941.

31. Spiegel, E. A., and Sommer, I.: Neurology of the Eye, Ear, Nose, and Throat, New York, Grune & Stratton, Inc., 1944.

32. Torkildsen, A.: En statistisk belysning av 353 delvis vertifiserte tilfelle av intrakraniell tumor, Norsk mag. lægevidensk. 99:137 (Feb.) 1938.

33. Torkildsen, A.: Ein Beitrag zur Klinik der Frontaltumoren, Zentralbl. Neurochir. 2:291-300 (Jan.) 1938.

34. Torkildsen, A.: Frontale intracranielle avulsters klinik, Norsk mag. lægevidensk. 99:310-325 (March) 1938.

35. Torkildsen, A.: Nogen bemerkninger om svulster i bakre skallegrop, Norsk mag. lægevidensk. 99:495-511 (May) 1938.

36. Torkildsen, A.: Om funn og symptomer ved temporale og occipitale tumores, Norsk mag. lægevidensk. 99:996-1013 (Sept.) 1938.

37. Voris, H. C., and Adson, A. W.: Tumors of the Corpus Callosum: Pathologic and Clinical Study, Arch. Neurol. & Psychiat. 34:965-972 (Nov.) 1935.

38. Voris, H. C.; Adson, A. W., and Moersch, F. P.: Tumors of the Frontal Lobe: Clinical Observations in a Series Verified Microscopically, J. A. M. A. 104:93-99 (Jan. 12) 1935.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

THE ELECTROMYOGRAM IN MYXEDEMA. S. S. WALDSTEIN, D. BRONSKY, H. B. SHRIFTER, and Y. T. OESTER, A. M. A. Arch. Int. Med. 101:97 (Jan.) 1958.

The authors conducted electromyographic studies upon 20 patients with myxedema and 6 patients with thyrotoxic myopathy. The latter group showed no abnormal findings, but the patients with myxedema displayed altered electrical activity of the musculature, which could be divided roughly into four different patterns: (*a*) polyphasic motor-unit action potentials; (*b*) low-voltage, irregularly timed potentials of short duration following voluntary motion; (*c*) irregular potentials of excessive voltage outlasting by several times the electrode movements or reflex hammer stimulus, and (*d*) repetitive potentials following reflex motion. The abnormalities vanished after successful treatment of the myxedema. Slow, prolonged muscle contraction with delayed relaxation is considered to be one of the most characteristic clinical diagnostic features of myxedema. This muscular reaction is to be differentiated from the myotonic reaction, which may rarely coexist.

PARSONS, Montrose, N. Y.

STUDIES IN HEADACHE MECHANISMS. A. M. OSTFELD, H. GOODELL, and H. G. WOLFF, A. M. A. Arch. Int. Med. 101:755 (April) 1958.

The authors summarize the results of a number of their recent studies of tissue changes accompanying migraine which tend to suggest the pharmacologic properties of the pain-threshold-lowering substance active in the attacks. Some of the physiologic characteristics of this substance include its capacity for producing vasodilatation, increasing vascular permeability and tissue vulnerability, and lowering pain thresholds for relatively prolonged periods of time. Pharmacologically, the substance is water-soluble, is contained in ultrafiltrate, and is antagonized neither by antihistaminics nor by atropine. These features are exhibited by extracts of subsurface edema fluid appearing in relation to migraine attacks, as well as by certain known pain initiators, such as serotonin and bradykinin.

PARSONS, Montrose, N. Y.

SERUM MAGNESIUM IN RENAL DISEASES. W. O. SMITH and J. F. HAMMARSTEN, A. M. A. Arch. Int. Med. 102:5 (July) 1958.

Serum magnesium determinations were conducted on four groups of subjects: normals, patients with renal disease without azotemia, patients with renal disease with azotemia and without central nervous system depression, and uremic patients with central nervous system depression. In the last two groups only there was found to be a significant elevation in serum magnesium which correlated closely with the NPN and with EKG signs of depression of the conduction system. The level of magnesium could also be correlated with signs of central nervous system depression, such as listlessness, stupor, and coma. Inasmuch as magnesium is frequently given to reduce intracranial pressure in patients having "pseudouremic" syndrome, it is well to distinguish this condition from uremia, in the presence of which magnesium administration may lead to disastrous results. In the treatment of cerebral depression due to uremia itself, the use of magnesium is distinctly contraindicated. Patients with renal involvement not associated with azotemia may have hypomagnesemia, which produces a neurologic syndrome consisting of tremor, athetosis, and confusion, a picture encountered in three patients studied in this group. This condition may be ameliorated by the administration of magnesium.

PARSONS, Montrose, N. Y.

ENEMA INDUCED POTASSIUM LOSS IN PATIENTS WITH DISEASES OF THE SPINAL CORD AND CAUDA EQUINA. F. PLUM and M. F. DUNNING, Am. J. M. Sc. 233:387 (April) 1957.

Enema returns from 8 control patients, 10 patients with paraplegia, 18 patients with poliomyelitis, and 2 patients with cauda equina lesions were analyzed for potassium. Tap water was used for the enemas. Patients with spinal-cord or lumbosacral-nerve-root disease lost twice as

much potassium in their stool as did normal subjects. Despite K loss in the stool, the neurological patients showed no tendency to conserve K in subsequent enema evacuations, and there was not sufficient reduction of urinary excretion of K to prevent a reduction in serum K. The increased volumes of fluid and the greater time required to effect bowel evacuation may have contributed to the K loss. The present study demonstrates the need for early bowel training of such patients to avoid stool potassium losses by enemas.

BERLIN, Mount Vernon, N. Y.

EFFECT OF FOCAL INTRACRANIAL LESIONS ON HIGH BLOOD PRESSURE. A. M. OSTFELD, Am. J. M. Sc. 235:539 (May) 1958.

The functioning of the brain has been implicated as a significant factor in the genesis of high blood pressure. In order to test this thesis, the author studied a group of 14 untreated hypertensive patients. Two had had frontal lobe and two temporal lobe excisions; five had meningioma; two had acoustic neurinoma, and three had cerebral vascular lesions. An exploration of the brain had been carried out in 13 cases. There were no indications that there existed other than "essential" causes of hypertension. The presence of the cerebral lesion did not alter renal function even in those instances in which altered mentation resulted in apathy and lowered drive. In two subjects who did develop a lowering of blood pressure following the cerebral lesions, there was personality and intellectual deterioration. Two subjects with bifrontal lesions and one with acoustic neuroma exhibited elevations of blood pressure after stress interviews, but one subject with a large parietal and another with a bifrontal lesion exhibited no such response. In two subjects whose hypertension persisted, after cerebral lesions, ganglion-blocking agents lowered the blood pressure. The thesis is advanced that no one part of the cerebral cortex is preeminently important in mitigating or maintaining hypertension or the capacity to respond to stressful events with pressor episodes.

BERLIN, Mount Vernon, N. Y.

THE RELATION OF DIETARY PYRIDOXINE TO THE 5-HYDROXYTRYPTOPHAN DECARBOXYLASE ACTIVITY OF RAT KIDNEY. J. A. BUZARD and P. D. NYTCH, J. Biol. Chem. 229:409 (Nov.) 1957.

Since 5-hydroxytryptophan decarboxylase occurs in brain, it is of interest that Buzard and Nytch found the enzyme in rat's kidney to be a typical pyridoxal phosphate requiring one. It is somewhat less sensitive to vitamin B_6 deficiency than cysteine sulfinic acid decarboxylase, but more sensitive than glutamic acid decarboxylase. Both the apoenzyme and the coenzyme activities of rat's kidney tissue are reduced by vitamin B_6 deficiency. The coenzyme activity is the more sensitive.

PAGE, Cleveland.

METABOLISM OF ESSENTIAL FATTY ACIDS: VII. CONVERSION OF γ-LINOLENIC ACID TO ARACHIDONIC ACID. J. F. MEAD and D. R. HOWTON, J. Biol. Chem. 229: 575, (Dec.) 1957.

Arachidonic acid is formed in the body by the addition of the two carbon atoms of acetate to the carboxyl group of linoleic acid and by the removal of four hydrogen atoms to form two additional double bonds. Mead and Howton found that when methyl γ-linolenate-1-C^{14} was fed to rats, the sole highly active fatty acid was arachidonic. The results support the view that γ-linolenic acid is an intermediate in the conversion of linoleic to arachidonic acid.

PAGE, Cleveland.

PRECURSORS OF SQUALENE AND CHOLESTEROL. F. DITURI, J. L. RABINOWITZ, R. P. HULLIN, and S. GURIN, J. Biol. Chem. 229:825 (Dec.) 1957.

2-C^{14}-Mevalonic acid is incorporated directly into squalene and cholesterol by rat liver homogenates with little randomization of isotopes before polymerization. Synthetic 3'-C^{14}-3-hydroxy-3-methylglutaric acid is not so incorporated. The previously reported biological activity of this substance may be attributed to an unidentified impurity. Further, it has been shown that mevalonic acid is incorporated into farnesenic acid by rat liver enzymes, and that C^{14}-farnesenic acid is incorporated into cholesterol.

PAGE, Cleveland.

SOLUBLE MONOAMINE OXIDASE: ITS PROPERTIES AND ACTIONS ON SEROTONIN. H. WEISSBACH, B. G. REDFIELD, and S. UDENFRIEND, J. Biol. Chem. 229:953 (Dec.) 1957.

A purified monamine oxidase from guinea pig liver converts serotonin to 5-hydroxyindoleacetic acid via 5-hydroxyindoleacetaldehyde. The aldehyde is then converted to the acid by a

diphosphopyridine nucleotide (DPN)-linked system. Quantitative conversion of serotonin could be obtained. The substrate specificity of the soluble enzyme was similar to that of mitochondrial monamine oxidase.

PAGE, Cleveland.

L-CYSTATHIONINE IN HUMAN BRAIN. H. H. TALLAN, S. MOORE, and W. H. STEIN, J. Biol. Chem. *230*:707 (Feb.) 1958.

Tallan, Moore, and Stein have shown the presence of L-cystathionine in extracts of human brain in concentrations ranging from 22.5 to 56.6 mg/100 gm. wet weight of tissue. Human liver, kidney, and muscle contain less than 1 mg. % of cystathionine. Other species contained less than 4 mg. %, except the brains of rhesus monkeys, which contained 12.8 mg. %. The brain of the horseshoe crab, in contrast, contained 15 mg. %, but the concentration of nearly all of the accompanying amino acids was nearly tenfold that found in brains of other species. This is the first demonstration that cystathionine is a normal constituent of mammalian tissue. Cystathionine is found in the metabolic conversion of methionine to cysteine.

PAGE, Cleveland.

THE ENZYMATIC FORMATION OF LECITHIN FROM CYTIDINE DIPHOSPHATE CHOLINE AND D-1,2-DIGLYCERIDE. S. B. WEISS, S. W. SMITH, and E. P. KENNEDY, J. Biol. Chem. *231*:53 (March) 1958.

Previous work has shown the function of cytidine coenzymes in the enzymatic synthesis of lecithin, phosphatidylethanolamine, and sphingomyelin. The present study describes some of the properties of phosphorylcholine-glyceride transferase, which catalyzes the reaction converting cytidine diphosphate choline and D-1, 2-diglyceride to lecithin. The enzyme used was the particulate fractions from chicken or rat liver containing both mitochondria and microsomes.

PAGE, Cleveland.

CHEMICAL NATURE OF MONOPHOSPHOINOSITIDES. D. J. HANAHAN and J. N. OLLEY, J. Biol. Chem. *231*:813 (April) 1958.

The phosphoinositides have not been a clearly defined group in the family of lipids. Hanahan and Olley have studied the chemical nature of highly purified, metal-containing monophosphoinositides of rat and beef liver and yeast. Hydrolysis yielded glycerides and inositol monophosphate. The most probable structure, derived from a variety of optical measurements, is a diacyl derivative of glycerylphosphorylinositol (phosphatidyl inositol).

PAGE, Cleveland.

THE QUANTITATIVE HISTOCHEMISTRY OF THE BRAIN: V. ENZYMES OF GLUCOSE METABOLISM. M. V. BUELL, O. H. LOWRY, N. R. ROBERTS, M. W. CHANG, and J. J. KAPPHAHN, J. Biol. Chem. *232*:979 (June) 1958.

Micromethods validated for use on frozen-dried brain have been devised for measurement of hexokinase, phosphoglucoisomerase, phosphofructokinase, glycogen phosphorylase, and phosphoglucomutase in 1μg. or 2μg. of tissue. These, combined with existing methods for aldolase and glucose-6-phosphate dehydrogenase, have been used to measure seven major enzymes of hexose metabolism in five white tracts, two molecular layers, two layers of cell bodies, and a layer of packed dendrites from rabbit brain. Those enzymes were lower in cell-body layers than in other gray areas, while white tracts varied greatly among themselves. Heavily myelinated tracts are low in hexokinase activity but rich in glucose-6-dihydrogenase. The other five enzymes were about as active on a fat-free dry-weight basis as the cell-body layer. The enzymes of hexose metabolism tend to vary in a parallel fashion.

PAGE, Cleveland.

A STUDY OF A MUCOLIPIDE FROM OX BRAIN. A. ROSENBERG and E. CHARGAFF, J. Biol. Chem. *232*:1031 (June) 1958.

"Mucolipids" are defined as water-soluble lipid polymers of high molecular weight containing fatty acid, a sphingosine-like base, hexose, amino sugar, sialic acid or related substance, and sometimes additional components, such as peptides. A complex ampholytic mucolipid has been isolated from ox brain which is homogeneous under electrophoresis and ultracentrifugation. The calculated molecular weight is 180,000. The number of component molecules per mucolipid molecule is as follows: fatty acid (mainly lignoceric), 101; sphingosine, 99; hexose (galactose and glucose, and the ratio of 8:1), 234; ovine sialic (*N*-acetylneuraminic) acid, 151, *N*-acetylgalactosamine, 36, and amino acid, 58.

PAGE, Cleveland.

THE ENZYMATIC SYNTHESIS OF SPHINGOSINE. R. O. BRADY and G. J. KOVAL, J. Biol. Chem. 233: 26 (July) 1958.

Enzyme preparations from rat brain are able to incorporate L-serine-U-C^{14} or DL-serine-3-C^{14} into Carbons 1 and 2 of sphingosine. Carbons 3 to 18 originate from palmityl coenzyme A. Sphingosine synthesis requires reduced triphosphopyridine nucleotide, pyridoxal phosphate, and manganese ions. An enzyme has been found in brain which catalyzes the reduction of palmityl coenzyme A by reduced triphosphopyridine nucleotide. The primary product of the condensing reaction appears to be dihydrosphingosine. The demonstration of the enzymatic reduction of Safranin T but not diphosphopyridine nucleotide by dihydrosphingosine suggests that the oxidation of dihydrosphingosine to sphingosine is catalyzed by a flavoprotein.

PAGE, Cleveland.

THE ACTIVATING EFFECT OF ADENOSINE TRIPHOSPHATE ON BRAIN ADENYLIC DEAMINASE. J. MENDICINO and J. A. MUNTZ, J. Biol. Chem. 233:178 (July) 1958.

Acetone extracts of dog brain contains an enzyme capable of deaminating adenosine-5′-phosphate only in the presence of adenosinetriphosphate. It has been purified twentyfold and has been shown to have an absolute requirement of relatively high levels of ATP, which has a specific activating effect not attributable to catalytic quantities of other contaminating triphosphates. Experiments with P^{32} labeled adenosine-5′-phosphate show it to be the direct source of the inosinic acid formed. ATP is recovered at the end of the reaction.

PAGE, Cleveland.

NEUROLOGICAL LESIONS IN CATS FOLLOWING CEREBROSPINAL FLUID MANIPULATION. R. P. BUNGE and P. H. SETTLAGE, J. Neuropath. & Exper. Neurol. 16:471 (Oct.) 1957.

Thirty-one cats were subjected to various forms of cerebrospinal fluid barbotage in an attempt to explain partial paralysis of the posterior extremities noted in previous experiments. The animals were anesthetized, and a 20-gauge needle was introduced into the cisterna magna. The experimental procedure involved withdrawal and reinjection of cerebrospinal fluid through the cisterna puncture needle. One cubic centimeter was gently aspirated over 2 to 3 minutes and, after 5 minutes, was reinjected forcibly in 10 seconds, this procedure being repeated 5 to 25 times. Several interesting findings were noted: 1. Of the 31 cats subjected to forced CSF injection, 15 developed definite and lasting neurological deficits, varying from near-complete to frank but minor disturbances in gait involving only the posterior extremities, with no alteration to painful stimuli and no muscle atrophy. 2. The neurological deficiency occurred maximally during the second postoperation week. 3. No correlation was noted between the number of times 1 cc. of fluid was exchanged and the resultant neurological deficit. 4. The amount of CSF exchanged did not necessarily determine the amount of damage. 5. Almost without exception, all animals demonstrated some improvement after suffering an initial maximal neurological deficit. 6. Neuropathologic studies indicated a shallow band of demyelination of the white matter over the periphery of the upper spinal cord and lower medulla—that part of the central nervous system directly related to the puncture site. This was followed in 120-300 days by evidence of reconstruction of myelin sheaths in these areas. The authors suggest that cystic fluid pockets in the subdural or subarachnoid space may have compressed the surface structures of the cord and brain stem, or that the cerebrospinal fluid might be rendered toxic by the pumping procedures.

AIGNER, Rochester, Minn.

5-NUCLEOTIDASE IN NORMAL AND DISEASED HUMAN SKELETAL MUSCLE. E. B. BECKETT and G. H. BOURNE, J. Neuropath. & Exper. Neurol. 17:199 (April) 1958.

Using a special technique, the authors attempted to demonstrate the enzyme 5-nucleotidase in human skeletal muscles derived by biopsy. In normal muscle little or no enzyme activity was shown—any activity present was entirely restricted to connective tissue elements. There was an increase of the enzyme activity whenever muscle fiber atrophy and destruction, with replacement by dense connective tissue, was present, irrespective of clinical diagnosis. The possibility of using 5-nucleotidase-activity inhibitor in cases in which the enzyme was increased is suggested.

AIGNER, Rochester, Minn.

LIVER FUNCTION AND LIVER TREATMENT IN ENDOGENOUS PSYCHOSES. G. YASARGIL, Psychiat. et neurol. 135:401 (June) 1958.

Yasargil assessed liver function in a group of 274 psychotic patients by means of the hippuric acid clearance test. It was found to be pathologic in 72% of patients with so-called

endogenous psychoses (schizophrenia, manic-depressive psychosis, involutional and reactive depressions, etc.), and only one factor, namely, the degree of severity of the mental disorder, could be correlated with the disturbance in liver function as measured by this test. For over 90% of the most disturbed patients the results of the hippuric acid excretion test were either positive or suggestive, as compared with 8% of the "quiet" groups. This observation held true for patients receiving various forms of treatment, including electroconvulsive and insulin coma therapy, as well as leukotomy. A group of 82 patients received longitudinal studies showing alterations in liver function tests paralleling the fluctuations in mental state, occurring either spontaneously or in association with one or another of the above forms of treatment. These findings, which are assumed to reflect an expression of metabolic change seen in the disturbed phases of mental illness, are of particular interest, in view of the unencouraging results obtained by investigators who have previously attempted to treat these psychoses by the use of liver preparations.

PARSONS, Montrose, N. Y.

MOTOR CONDITIONING DURING THE WAKING STATE AND SLEEP: ELECTROENCEPHALOGRAPHIC STUDY IN NORMAL MAN. A. ROGER, E. M. SOKALOV, and L. G. VORONIN, Rev. neurol. 96: 460 (June) 1957.

Twelve normal subjects, students at the University of Moscow, 18 to 23 years of age, were studied to ascertain the variations in EEG, cardiac rhythms, psychogalvanic responses, and electromyograms in response to visual and proprioceptive stimuli. After a period in which these two stimuli were presented in random sequence, the visual stimulus was presented for four seconds, and then for the next three seconds the visual stimulus was presented while the right hand was being passively extended. Motion of the hand initially had a diffuse effect on the EEG, but after a variable number of repetitions the excitatory reaction at the Rolandic region was blocked. Visual stimulation applied to subjects with eyes closed readily blocked the rhythms of the parieto-occipital and Rolandic regions. Repetitive visual stimuli were less effective than proprioceptive stimuli in blocking cerebral rhythms. When the stimuli were combined, the visual stimulus was without effect on the EEG, and not until the proprioceptive stimulus was introduced was there a blockage of the EEG, in 19 out of 30 trials. Repetitive stimulation, visual and/or proprioceptive after a period of habituation, induced a state of cortical inhibition characterized by slow waves. During the slow-wave activity, visual stimuli had no effect, but proprioceptive stimuli evoked alpha activity posteriorly and beta activity in the Rolandic area, lasting 5-15 seconds after cessation of stimulation. It was inferred that there is a diffuse, nonspecific primitive system contributing a "cortical tonus" essential for conditioning and dependent on the excitatory inhibitory effects of subcortical centers.

BERLIN, Mount Vernon, N. Y.

DISTURBANCE OF CEREBRAL BLOOD CIRCULATION IN ACUTE STAGE OF MYOCARDIAL INFARCTION, M. J. MELIKOVA, Klin. med. 4:23, 1956.

The relationship between the acute vascular disturbances in the myocardium in the presence of an infarction and the disturbance of the cerebral blood circulation was investigated. To this end, 130 case reports of patients with myocardial infarction were studied, and clinical examinations were carried out in 14 patients with myocardial infarction accompanied by disturbances of the cerebral blood circulation. In 9 out of 13 cases ending in death, examination of the brain was performed. The regularity of vascular disturbances in the brain during the acute stage of myocardial infarction was established. Besides slight, transient neurological symptoms, gross organic disturbances of the CNS functions were observed, which sometimes masked the clinical picture of the acute heart lesion. The histological examinations of the brain in each case revealed morphological changes in the vessels during the acute stage of myocardial infarction. Marked fluctuations of tone and increase of permeability, with extravasations of plasma and diapedetic hemorrhages, were found. The changes in the nerve cells and glia are secondary and caused by oxygen deficiency and cerebral edema. The morphological changes are uniform and more marked in cases of hypertension than in cases of normal blood pressure. The prominence and character of the cerebral disturbances show that the angioplastic changes depend on neurohumoral factors caused by the heart lesion and also by atherosclerosis of the brain vessels.

APROSINA, Moscow.

Effect of Vestibular Stimulation of the Opticospatial Perception in Focal Lesions of the Cerebral Cortex. Z. S. Bein and F. M. Loselevich, Zhur. nevropat. i psikhiat. 57:34, 1957.

A study was made of the role of the vestibular apparatus in various types of disturbance of opticospatial analysis and synthesis due to lesions of the parieto-occipital cortical systems. For this purpose psychological and specialized otoneurological investigations (calorization and rotation) were performed on patients with focal traumatic lesions of the left cerebral cortex. On stimulation of the vestibular apparatus, all these patients showed slowing of their psychic reactions. In parieto-occipital localization of the lesion a transient deterioration of opticospatial perception was a characteristic feature. Patients with lesions of the temporofrontal and parietal regions showed no obvious changes in opticospatial perception, in spite of the appearance (as a result of stimulation) of vertigo. In patients with compensated (by means of special remedial instruction) disturbances, stimulation of the vestibular apparatus evoked transient failure to compensation. In slight degrees of disturbance of opticospatial perception, stimulation of the vestibular apparatus temporarily improved this perception, as a result of the influence of frontal afferentation. These findings confirm the existence of a most intimate connection between the vestibular system and the parieto-occipital areas of the cortex.

Golland, Moscow.

Neuropathology

Primary Reticulum-Cell Sarcoma of the Leptomeninges. C. A. Kane and J. M. Foley, A. M. A. Arch. Int. Med. 101:333 (Feb.) 1958.

Kane and Foley report a 62-year-old patient with reticulum-cell sarcoma simulating chronic meningitis and presenting a nonspecific clinical picture of headache and progressive dementia. Pathological findings included massive perivascular and perineural leptomeningeal infiltration with sheets of reticulum cells involving vessels and sparing dura and the systemic lymphoid system. The differential diagnosis is that of chronic meningitis, such as that due to tuberculosis and fungus disease, as well as metastatic carcinoma.

Parsons, Montrose, N. Y.

Histology of the Glioma of the Optic Nerve: A Study with Silver Carbonate. L. Liss and J. R. Wolter, A. M. A. Arch. Ophth. 58:689 (Nov.) 1957.

Liss and Wolter report on the histology of glioma of the optic nerve as worked out with the silver carbonate method. The pathologic material was obtained from a tumor of the left optic nerve in a 4½-year-old child. The cellular elements which formed the tumor were of three types: (1) elongated, or spindle-formed, mostly bipolar, Schwann elements; (2) round, multipolar oligodendrocytes, and (3) cells of the astrocyte series, particularly astroblasts. The commonest cells were those of the Schwannoid type, which are identical with the long cells of Hortega. In addition, there were numerous forms which mimic oligodendrocytes of Type I and other definitely identified as blastomatous oligodendroblasts. A third variety was less well differentiated—they were large elements similar to astroblasts.

Spaeth, Philadelphia.

Chordoma—Uncommon Destructive Lesion of Cerebrospinal Axis. C. M. Greenwald, T. F. Meaney, and R. C. Hughes, J. A. M. A. 163:1240 (April 6) 1957.

Greenwald and his co-workers illustrate the difficulty of making a diagnosis of chordoma by describing the roentgen findings in 20 cases. In 10 cases the lesions arose from the base of the skull; 6 lesions were vertebral, and 4, sacrococcygeal. Chordoma is an uncommon neoplasm of notochordal origin that must be considered in diagnosis of the destructive lesions occurring from the base of the skull to the coccyx. The clinical findings will vary with the level of the lesion, as will the differential diagnosis. Symptoms are of long duration, and a preoperative diagnosis is uncommon. The vertebral location is least common; however, this was not true in this series. The radiographic findings in chordoma are not diagnostic at any level and are most variable in the vertebral lesion. The variable features include site, extent, and direction of growth, degree of bony destruction, the soft-tissue component, the osteolytic or osteoblastic nature of the lesion, and the condition of the interspace.

Alpers, Philadelphia.

PROGRESSIVE DETERIORATING DISEASES OF INFANCY: FIRST COMMUNICATION. C. BENDA and J. C. MELCHIOR, J. Neuropath. & Exper. Neurol. 17:205 (April) 1958.

Among the various factors which eventually lead to severe mental deficiency in infancy and childhood, the progressive deterioration of initially normal-appearing infants presents great difficulties to the clinician and the neuropathologist. Apparently, not the result of prenatal developmental disorders nor the product of birth injuries or postnatal infectious processes, these deficiencies are often termed idiopathic, even though a metabolic disorder may be suspected.

The authors report three cases of progressive deterioration in initially normal infants, all associated with seizures, blindness, and tetraplegia. The first two are in siblings; the third involved one of two siblings, the other sibling being reported as normal. The third patient had a cherry-red spot in the retina, suggestive of amaurotic idiocy. The three patients died under the age of 5 years. The varying durations of illness revealed that the pathologic process was present at a different stage of development in each case. Histopathologic studies revealed in Cases 1 and 3 a leukoencephalopathy, with almost complete demyelination of white matter in the patterns usually referred to as Schilder's. The second case revealed less demyelination, but it was localized, representing a type of multiple sclerotic patch. The gray matter in the third case represented histologically Tay-Sachs amaurotic idiocy.

Although the cases are not intended to represent the same metabolic disease, they do suggest a search for a common denominator involving both white and gray matter—probably of the nature of a genetic enzyme, which affects the whole nervous system in the process of its building up and maintenance.

AIGNER, Rochester, Minn.

SOME OBSERVATIONS ON THE CONGENITAL DEFORMITY OF THE CENTRAL NERVOUS SYSTEM KNOWN AS THE ARNOLD-CHIARI MALFORMATION. P. M. DANIEL and S. J. STRICH, J. Neuropath. & Exper. Neurol. 17:255 (April) 1958.

Daniel and Strich discuss the anatomical findings in 26 cases of the Arnold-Chiari deformity. The cases included 15 male and 11 female infants, ranging from stillborn to the age of 22 months. The typical findings are as follows: 1. A "tail" of cerebellar tissue is displaced into the cervical region of the vertebral canal. This is the nodule of the vermis and not herniated tonsil. In one case it was 4 cm. long, reaching the level of the seventh cervical vertebra, while in others it was only a short, thick process of cerebellum. 2. Marked elongation and downward displacement of the brain stem involve chiefly the medulla and fourth ventricle but include also the pons, which is often flat and hardly distinguishable from the medulla. The brain stem extends into the spinal canal irrespective of whether the "tail" is long or short. 3. Frequently the gracile and cuneate tubercles are bent back upon themselves, overlapping the dorsal aspect of the cord and thus flattening it. 4. In all cases the cervical nerve roots are crowded and take an ascending course. Also, the cranial nerves run in a much more rostral direction and are longer than usual, especially the sixth. 5. The tectal plate is often sloped like a beak, the apex of which is formed by the inferior colliculus. 6. The amount of hydrocephalus varies from slight to gross dilatation of the lateral ventricle. 7. The posterior fossa is much smaller than normal, with low attachment of the tentorium cerebelli, often to the margin of the foramen magnum. 9. All cases had a spina bifida and myelomeningocele. 10. Eleven cases showed hypertrophy of the bladder without obstruction. The authors suggest that the abnormalities in the central nervous system develop early in embryonic life and that the elongation of the brain stem may be due to the failure of the pontine flexure to form. Clinically, the authors suggest that this deformity should be considered in any infant with a meningocele or, particularly, a meningomyelocele. Also, the dangers of attempting cisternal puncture in such infants is obviously dangerous.

AIGNER, Rochester, Minn.

STUDIES ON MULTIPLE SCLEROSIS: I. MULTIPLE SCLEROSIS VIEWED AS A "CHRONIC DISSEMINATED ENCEPHALOMYELITIS." II. ETIO-PATHOGENESIS OF MULTIPLE SCLEROSIS (INFECTIOUS ALLERGIC OR TOXIC ALLERGIC). A. FERRARO, J. Neuropath. & Exper. Neurol. 17:278 (April) 1958.

Ferraro supports the idea that no appreciable differences exist between acute multiple sclerosis, the early stages of multiple sclerosis, and the acute or subacute varieties of the disseminated encephalomyelitides. In the last category he includes (*a*) the encephalomyelitides

following infectious exanthematoid diseases in children (measles, varicella, variola, scarlet fever, rubella, etc.); (*b*) those following generally mild infectious conditions (influenza, coryza, pneumonia, etc.) in children and adults; (*c*) spontaneous encephalomyelitis not clearly related to definite etiologic agents, and (*d*) the forms following antismallpox and antirabies vaccination. The differentiation which relied primarily on the value of a history of relapses and remissions which were seen in multiple sclerosis has lost its importance, since such remissions may occur also in the various types of acute disseminated encephalomyelitis. Pathologically, no appreciable differences exist among the lesions of acute disseminated encephalomyelitis, the postvaccinal encephalomyelitides, acute multiple sclerosis, and the acute foci related to relapses in chronic multiple sclerosis. The author proposes, therefore, to label multiple sclerosis as a "chronic variety of disseminated encephalomyelitis." Multiple sclerosis may then represent the chronic stage of an acute disseminated encephalomyelitis, and not a transformation from one disease into another. He also feels that immunobiological factors determine whether a case will be a simple acute and reversible encephalomyelitis or a chronic, progressive process. As for etiopathogenesis, the author proposes a common ground, which he calls infectious-allergic or toxic-allergic. The toxic or infectious etiologic agent may vary in different groups of cases, but in all it must combine with a partial antigen to create a complete "demyelinating encephalogenic antigen," which will trigger off an allergic reaction. Therefore the ultimate pathogenic mechanism responsible for the clinicopathologic changes will remain an allergic one.

AIGNER, Rochester, Minn.

POLIOENCEPHALOMYELOPATHY REMINISCENT OF CREUTZFELDT-JAKOB'S SYNDROME: A CLINICO-PATHOLOGIC REPORT OF A CASE. G. A. SCHWARZ and L. J. BARROWS, J. Neuropath. & Exper. Neurol. 17:352 (April) 1958.

Schwarz and Barrows report a case of polioencephalomyelopathy which is consistent with Creutzfeldt-Jakob syndrome. Their patient was a man who began to have his first neurologic disease in his early 50's. The difficulty began with diplopia and ataxia, which progressed to severe generalized incoordination with dysarthria, dysphagia, and nystagmus. Later in the course of the disease a diffuse muscle wasting, rigidity, and emotional disturbances appeared. No evidence of pyramidal involvement was seen.

Postmortem examination revealed no evidence of demyelinating disease. There was in the cerebellum almost complete absence of Purkinje cells and a diffuse thinning of the granule cells, without any inflammatory reaction. The midbrain, pons, and medulla oblongata revealed neuronal alterations and glial nodes scattered in these areas. These changes suggested more recent and persisting pathologic activity. There was also a highly developed reactive astrocytic change in the anterior horns, and in the thoracic cord perivascular infiltrations and neutral fat could be demonstrated, suggesting that the acute disease was continuing in this portion of the central nervous system. The cerebrum was essentially normal. The authors review the 31 cases of Creutzfeldt-Jakob syndrome which have been reported in the literature to date. The progressive destruction of neuronal groups with a remarkably abundant response of glia seen in their cases seemed to be the major feature of the pathology of this syndrome and is perhaps the chief similarity which ties the cases together. Clinically and pathologically, however, there are tremendous variations between the various cases in this category in the literature. It is suggested that the cases should not be considered a single disease entity and that this is not a disease but a syndrome, and should be so designated.

AIGNER, Rochester, Minn.

DEGENERATION OF THE BRAIN STEM RETICULAR FORMATION, OTHER PARTS OF THE BRAIN STEM AND THE CEREBELLUM: AN EXAMPLE OF HETEROGENOUS SYSTEMIC DEGENERATION OF THE CENTRAL NERVOUS SYSTEM. W. J. C. VERHAART, J. Neuropath. & Exper. Neurol. 17:382 (April) 1958.

Verhaart presents a case study of a patient with a chronic degenerative disease, starting at the age of 41, which in the course of the next nine years caused severe atrophy of the various parts of the central nervous system. Clinically, his difficulty began with psychiatric symptoms of paranoid delusions, for which he was placed in a mental hospital. There he became bedridden, demented, spastic-paretic in all four extremities, and severely dysarthric. One month prior to death he developed a mask-like face, total dysarthria, hypersalivation, and severe spasticity of all four extremities. Pathologic examination of the central nervous

system revealed almost total degeneration of the globus pallidus, the superior colliculus, the mesencephalic branch of the trigeminal nerve, the central cerebellar nuclei, the posterior commissure and its nuclei, the vestibular nuclei and, especially in the brain stem, the reticular formation. Other areas of the brain stem were less involved. This case of heterogenous (more than one system involved) degeneration was compared with 21 similar cases found in the literature, in which the degeneration was not fixed in type. The author feels that the anatomical interrelations alone are insufficient to explain the atypical distribution and that facilitation of normally unusual types of degenerations has to be taken into account. This facilitation can be brought about either by involvement of other parts of the system to which the part under consideration belongs, or by some special individual susceptibility to degeneration of such a nucleus. The unequal affection of the different parts of a system in typical cases was emphasized in order to exemplify variations in a typical case anatomically unaccounted for.

AIGNER, Rochester, Minn.

PROGRESSIVE MULTIPLE LEUKO-ENCEPHALOPATHY. K.-E. ASTRÖM, E. L. MANCALL, and E. P. RICHARDSON JR., Brain 81:93 (March) 1958.

The authors report three adult patients with an unusual demyelinating disease process, two of whom had chronic lymphatic leukemia and the third Hodgkin's disease. The neuropathological lesions were characterized by widely disseminated small oval perivascular foci of destruction of myelin sheaths, with relative sparing of axis cylinders. Plaque formation was present in some areas, particularly in the posterior parts of the cerebral hemispheres, where the damage was greatest, although all areas were involved. In addition to the myelin destruction, there was a distinctive cytological reaction, which consisted of hypertrophy of astrocytes into bizarre gigantic forms with mitotic figures, suggesting neoplastic cells in appearance, as well as oligodendrogliocytes with large round basophilic nuclei. The authors review the slides of five additional cases of Hodgkin's disease, sarcoidosis, and tuberculosis. It is believed that the neurological disease reported occurs as a complication of Hodgkin's disease or chronic lymphatic leukemia.

MANDEL, Philadelphia.

REPORT OF 2 CASES OF DEGENERATION OF THE CORPUS CALLOSUM AND THE QUESTION OF EXISTENCE OF MARCHIAFAVA-BIGNAMI DISEASE AS AN ENTITY. G. BOUDIN, J. BARBIZET, and S. BRION, Rev. neurol. 97:433 (Dec.) 1957.

Two cases are reported of the progressive development of severe persistent generalized rigidity and profound dementia in alcoholic patients. They remained in a vegetative state for one and three months, respectively, before death. There was severe necrosis of the entire corpus callosum. In addition, there were degeneration of the optic radiations, cellular loss in the cerebral cortex, a spongy degeneration with vascular proliferation in the mammillary bodies, and chromatolysis of the cells of the nuclei of Darkschewitsch and Edinger-Westphal, and an irregular loss of Purkinje cells. It is inferred that the syndrome of Marchiafava-Bignami is related to other alcoholic degenerations, such as that of Gayet-Wernicke.

BERLIN, Mount Vernon, N. Y.

A RARE MYCOSIS OF THE CENTRAL NERVOUS SYSTEM (MENINGOENCEPHALITIS CAUSED BY HISTOPLASMA CAPSULATUM). A. JUBA, Psychiat. et neurol. 135:260 (April-May) 1958.

Juba reports on a 33-year-old agricultural worker who developed a fulminant, nonbacterial meningoencephalitis, treated ineffectually with penicillin, chlortetracycline, and supportive measures. Autopsy findings included hemorrhagic endocarditis, adhesive pleuritis, and erosions of the gastric mucosa, in addition to changes in the nervous system consisting of a massive monocytic, primarily basilar meningeal reaction, extending into the adjacent neural parenchyma as miliary granulomata. The granulomata consisted of lymphocytes, monocytes, epithelioid cells, and fibroblasts surrounding necrotic centers or vessels. Within many of the above cells (especially swollen epithelioid cells) were noted round to oval Gram-positive bodies surrounded by pale borders and measuring about 1μ in size. Special fungus stains enabled identification of these intracellular structures as Histoplasma capsulatum. The portal of entry was not evident, but there was likelihood of involvement of the nervous system through hematogenous dissemination. The special vulnerability of agricultural workers to this condition was mentioned, and the author stressed the importance of considering fungous

infections in cases of meningoencephalitis where either the usual bacterial cultures of cerebrospinal fluid are sterile or inadequate response to antibiotic therapy is manifested.

PARSONS, Montrose, N. Y.

PATHOMORPHOLOGICAL CHANGES IN THE VESSELS OF THE BRAIN AND OTHER ORGANS IN STILLBIRTH DUE TO INTRAUTERINE ASPHYXIA. V. N. SHISHKOVA, Akush. i ginek. 33(2):8, 1957.

The internal organs and brains of 75 newborn infants dying of asphyxia were examined. It was established that blue asphyxia is the result of prolonged intrauterine oxygen starvation produced in the fetus by the transmission of infections incurred by the mother. The vascular pathology of the fetus in blue asphyxia is a secondary phenomenon. There is primarily an oxygen starvation, and later there ensue functional changes in the vessels of the brain and other organs (permeability of vessel walls, loss of tonus, perivascular hemorrhages, and perivascular edema). The absence of large hemorrhages and the presence of microfocal hemorrhages in the parenchyma of the brain are characteristic of blue asphyxia. A disturbance of the hemodynamics, as in shock, is the basis of white asphyxia, as confirmed by the presence of acute stasis in the capillaries while the large vessels are inadequately filled.

KRYMSKII, Moscow.

PATHOMORPHOLOGY OF MYCOSES OF THE CENTRAL NERVOUS SYSTEM. B. S. KHOMINSKII, Arkh. pat. 18(4):43, 1956.

Autopsy of 1,193 persons who died of various diseases of the central nervous system revealed two cases of brain affection with yeast-like fungi. The first was a man, aged 37, who became acutely ill after a chill and died three months later. "Tubercle"-like granulomata were detected in the brain. The lesions contained an abundant quantity of spores of the fungus and consisted of specific granulation tissue with epithelioid and giant cells and proliferation of argyrophilic fibers; leukocytic infiltrations and granular necrosis were seen in the central part of the granuloma. The second, a woman aged 61, had manifestations of diffuse affection of the cerebral meninges of one and one-half years' duration. Autopsy revealed thickening of the soft meninges of both hemispheres; microscopically, lymphocytic infiltrations of the meninges, together with fibroblasts and plasma and giant cells, containing yeast-like fungi, could be seen. The giant cells were arranged in layers in both cases. The inflammatory infiltrations diffused along the adventitia of the vessels into the brain cortex, forming microgranulomata of similar cell composition. Individual giant cells containing fungi were demonstrated in the lungs and tracheobronchial lymph nodes. Similar changes in the central nervous system are encountered frequently in torulosis caused by yeast-like fungi. Neither of the patients received antibiotic treatment. Spread of the fungus into the meninges and brain took place by the blood route.

URANOVA, Moscow.

SPONGIOBLASTOMA MULTIFORME. L. I. SMIRNOV, Zhur. nevropat. i psykhiat. 56:201, 1956.

Spongioblastoma multiforme was noted in 452 (8%) of 5,773 cases of brain and cord tumors seen at the Neurological Institute. These tumors constituted about 14% of all tumors of the nervous system of neuroectodermal origin (3,082 cases). From the histological standpoint the multiform spongioblastoma is characterized by marked changes in the nucleocytoplasmic ratio, in favor either of the nucleus or of the cytoplasm, with formation of giant cells; at the same time, processes of maturation, with the appearance of cell elements of macroglial nature, proliferation of mesenchyme with new-formed vessels, and hyperplasia of endothelium, were noted in the tumors, together with rapidly developing coagulative necroses unrelated to circulatory disturbances. The growth of the multiform spongioblastoma is associated with proliferation and abnormal hypertrophy of microgliocytes and extension of undifferentiated cell elements into the adjoining cerebral cortex. These groups of tumors studied can be divided into primary multiform spongioblastoma, with acute clinical course and simulating an inflammatory or a vascular disease, and the secondary type, developing from undifferentiated astrocytoma or oligodendroglioblastoma, with clinically discernible transition from benign to malignant neoplasia. In a third variety of spongioblastoma the author

includes those tumors with well-marked growth of mesenchyme. The macroglial nature of spongioblastoma multiforme was confirmed by tissue culture. The possibility of a viral etiology of the neoplasms is mentioned.

URANOVA, Moscow.

Psychiatry and Psychopathology

CONVERSION HYSTERIA IN CHILDHOOD. A. HINMAN, A. M. A. J. Dis. Child. 95:42 (Jan.) 1958.

Hinman notes that the frequency of conversion hysteria in children is difficult to estimate with any accuracy. It is certainly rare. It is felt, however, that the incidence is higher in the area (rural North Carolina) from which this report emanates. Here families live in semi-isolation and have a strong patriarchal control. The culture is unsophisticated and infantile and seems to predispose to hysteria. This study comprises 28 children—21 girls and 7 boys. The ages ranged from 4½ to 14 years, with the average about 10 years. Choice of symptoms included seizures, astasia-abasia, dysphagia, globus hystericus, abdominal pain, paresthesia, aphasia, hyperventilation, and polydipsia-polyuria, in declining order of frequency. Occasionally more than one symptom was present. The treatment of conversion hysteria is not simple. The symptoms must be reconverted before psychotherapy can be effective. A gentle and slow approach, with punitive aspects, is advised.

SIEKERT, Rochester, Minn.

OCCURRENCE AND MEANING OF DREAMS OF FOOD AND EATING: I. TYPICAL FOOD AND EATING DREAMS OF 4 PATIENTS IN ANALYSIS. W. W. HAMBURGER, Psychosom. Med. 20:1 (Jan.-Feb.) 1958.

Hamburger presents his interpretation of dreams of food and eating in patients undergoing analysis. These dreams occurred in obese and nonobese patients irrespective of their clinical problems. Dreams were studied of four female patients which dealt in their manifest content with food, eating behavior, or scenes relating to food and eating, such as kitchens, dining rooms, and restaurants. The patients were selected because they reported a large number of such dreams. The dreams were studied in relation to the analytic material immediately preceding and following such dreams. They were considered from the point of view of the latent dream wish, and also in relation to the dream ego and how this dealt with the wish through acceptance, distortion, and other dream work, as described by French. From the 229 dreams studied (the largest number being 115 from one patient), Hamburger arrived at the following conclusion: The most prominent latent meanings of this type of dream were (*a*) as a regressive substitute gratification for genital satisfaction and (*b*) as a symbol of pregenital fixations in maternal love, support, and reward. The author suggests that further study of such food dreams may shed light on disorders such as hysterical conversion symptoms, food preferences, idiosyncrasies, allergies, and certain psychosomatic disturbances which involve appetite and upper gastrointestinal functioning.

AIGNER, Rochester, Minn.

SEX CHROMATIN AND SEXUAL BEHAVIOR: A STUDY OF 36 MEN WITH FEMALE NUCLEAR PATTERN AND OF 194 HOMOSEXUALS. J. RABOCH and K. NEDOMA, Psychosom. Med. 20:55 (Jan.-Feb.) 1958.

Raboch and Nedoma report a study on the sex life of 36 men with a female type of sex chromatin and a study of 194 homosexual males. They attempt to deduce a causal relation between the process resulting in the female nuclear pattern and homosexuality in men.

The clinical study of the men included measurements of the long axis of each testis (the normal being greater than 3.4 cm.), examination of ejaculates, and testicular biopsy. The chromatin sex was determined by studies of buccal-mucosa epithelial cells. Of the 36 men with female nuclear patterns, 35 had hypoplastic testes, measuring between 1 and 2.6 cm. Bilateral cryptorchidism was found in the remaining patient. Of these patients, 17 had ejaculates of less than 1.5 cc.; 11 had between 1.5 and 3 cc., and 8 had more than 3 cc. The sexual trend was distinctly heterosexual in 32, and the remaining 4 were classified as infantile, with no interest in sex throughout their entire life. Biopsy of 11 patients revealed a picture typical of the so-called Klinefelter syndrome. Of the homosexual males, the sex chromatin was determined only on those with hypoplastic testes (less than 3.4 cm. in the long axis). Of nine such patients, six submitted to chromatin determination. Of

these six, all had the male nuclear pattern. Thirty-two other patients in the group were examined by Jirásek at random, and the male nuclear pattern was found in each one. In the discussion that follows, the authors distinguished two main periods of somatosexual development. The first takes place in the very young embryo and results in the nuclear pattern of the female type—this disturbance does not influence the sexual tendencies. The second period occurs in adolescence, when a degenerative process in the testes occurs, which results in lowered sexual activity. The authors feel that testicular androgens affect the development and course of sex life more effectively than factors producing the female nuclear pattern.

AIGNER, Rochester, Minn.

News and Comment

GENERAL NEWS

The American Academy of Neurological Surgery.—The fourth Annual Academy Award has been received by Dr. Norman Hill, Mayo Clinic, Rochester, Minn., for his paper entitled "Cerebrospinal Fluid Proteins, Glycoproteins, and Lipoproteins in Obstructive Lesions of the Central Nervous System."

The Academy announces its fifth Annual Award, which will be given for the best paper submitted reporting original clinical or laboratory investigation relating to the nervous system. The author shall have had principal responsibility for the investigation, and the paper shall not have been accepted for publication in a journal at the time it is submitted for the Academy Award. Eligibility is confined to doctors of medicine currently in training in neurological surgery, or to those who have completed training since June 30, 1957. Those certified by the American Board of Neurological Surgery, the Royal College of Surgeons of Canada, subspecialty neurosurgery, or other equivalent certifying board are ineligible.

The recipient of the Award will be invited to present his paper at the 21st Annual Meeting of the Academy at Pebble Beach, Calif., Oct. 18 to 21, 1959. Expenses to and from the meeting (from the port of entry to the United States if living outside the North American Continent), expenses while attending the meeting, and an honorarium of $100.00 will be paid the recipient.

Manuscripts should be sent to Dr. Robert McLaurin, secretary of the Academy, Cincinnati General Hospital, Cincinnati 29. These must be submitted before July 15, 1959. A résumé of the candidate's postdoctoral training must accompany the paper when submitted.

Books

BOOK REVIEWS

Chemical Concepts of Psychosis. By Max Rinkel, M.D., and H. C. B. Denber, M.D. Price, $7.50. Pp. 485. McDowell, Obolensky, Inc., 219 E. 61st St., New York 21, 1958.

This volume, edited by Max Rinkel and H. C. B. Denber, consists of fifteen chapters by different authors—a series of separate, unconnected communications, but united by a common theme and by the fact that they were presented at an international Congress in Zurich in 1957. Several of the chapters have already been published elsewhere, and the inquiry by a given author has subsequently been pushed further. Despite its belated appearance, this is an important volume, since it includes under one cover the views of most of those working in western countries who are interested in chemical concepts of the psychoses.

The main theme that runs through the book, and is exemplified in different ways by different authors, is that psychotic patients as a group, notably schizophrenic patients, exhibit manifestations of impaired cerebral function, as a result of circulating noxious humoral agents that originate outside the brain and interfere with its function, or as a sequel to some disturbance in metabolism in the brain cells per se that interferes with their integrative capacity.

The contributions are incisive and stimulating. Detailed data are not usually given, so that a critical appraisal of evidence is difficult. The chapters are essentially progress reports, and the progress is indeed exciting and with extremely important implications. Although some of the authors incline to accept the metabolic and pharmacologic peculiarities that they have observed in the body fluids of schizophrenics as relatively independent of the life experiences and stress endured by the patient, actually nothing presented detracts from the possibility that the impaired function is the result of one or a series of faulty adaptive arrangements elaborated during prolonged exposure to circumstances perceived as threatening and involving either organs other than the brain or the brain itself.

Hoff points out that what is termed schizophrenia in the United States may be different from schizophrenia in Austria, and that the Austrian concept may even differ from that in neighboring Germany or Switzerland. Whatever its cultural manifestations in different countries, he suggests that there is a common basis to the various forms and concepts of schizophrenia and urges a standardization of nomenclature. He also postulates that defective enzymes are to blame for schizophrenia, but only those present in very small amounts, and responsible for the functions—not the maintenance—of the cells. This reviewer shares the opinion that the either- or attitude concerning the psychoses is uncalled for and impedes progress.

Various investigators emphasize the likelihood that the primary defect has to do with faulty detoxication, perhaps in the liver, or faulty metabolism of adrenalin, noradrenalin, serotonin, or acetylcholine. There is hardly a general statement at any point in this book that is not contradicted at some other point. For example, Thuillier notes that both a lack and an excess of serotonin have been blamed for inducing psychosis. He found a seemingly simple pair of relationships: Mescaline is a potentiator of serotonin's effects, while LSD is an antagonist. But further research showed that in the test tube LSD is also a potentiator in small doses, and an antagonist only in larger doses.

Heath reports on his group's highly provocative work with taraxein, a still unidentified substance extracted from the blood of schizophrenics but not yet found in that of persons free of the disease. Heath reports giving taraxein to twenty-six subjects. Four of these were schizophrenics with their disease in remission; the others were healthy persons from the population at large, or convict volunteers. Definite symptoms were induced in twenty-two; in four no change was noted. From 400 ml. of serum of schizophrenics 1.5 to 5 ml. of solution were obtained. This was injected intravenously. Control injections were made of solutions extracted from serum of nonpsychotic subjects. The double-blind technique, in which neither the investigators nor the subjects knew what substance was administered until the test was over, was adopted. Isotonic saline, ceruloplasmin, and amobarbital (Amytal) sodium were also used as controls for the taraxein. "Blocking and thought deprivation developed. All subjects were autistic and complained of depersonalization. They appeared dazed." Other symptoms, such as

"catatonic stupor and excitement" and "auditory hallucinations," occurred in subjects who received the active material but in none who received the placebos.

Also, corrective communications are already in evidence. Thus, the Akerfeldt simple test for mental disease, based on the presence of increased amounts of ceruloplasmin in the blood serum, is found by McDonald to be in no sense specific to schizophrenia.

From the spinal fluid of schizophrenics Bulle got a substance which, according to him, is indistinguishable from serotonin; the quantities varied directly with the severity of the disease. (From normal subjects he could get none.)

Recent work by Chapman, from the reviewer's laboratory, not included in this series of papers, demonstrates evidence of excessive proteolytic activity in the spinal fluid of patients with schizophrenia. The abnormality defined is in no sense specific to schizophrenia but is also present in the spinal fluid of patients with inflammatory and progressive degenerative process of the nervous system, as well as during excitation and after convulsions. The protease acts on globulin to produce a vasodilator substance which contracts the isolated rat uterus. Starch-gel electrophoresis of normal serum incubated with such spinal fluid indicates that the alpha-beta bands of serum are attacked by the enzyme. An abnormal fast gamma band is present in the spinal fluid protein of patients with schizophrenia.

Winter and Flataker bring evidence that biologically active substances are present in the blood and urine of the majority of schizophrenic patients and are absent in nonschizophrenic subjects. Whether these substances are the cause of the syndrome or end-products of a deranged metabolism which accompanies the disorder cannot now be defined. Thus probably many metabolic deviations will eventually be shown to be associated with the varied forms of schizophrenia and other psychoses.

Regardless of the mechanisms or chemical agents involved, the facts contained in this volume must have an important impact upon the teaching and orientation of the next generation of psychiatrists.

The papers in this book can be understood by anyone trained in the biologic sciences. It is warmly recommended to those interested in the psychoses, behavior, and brain function.

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Personality Growth in Psychiatric Residents

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In the three years of residency training, a physician is made into a psychiatrist. It is easy to think of this as a simple process, much like any other education: A group of people who want to learn a body of knowledge and skills are offered opportunities for such learning, and learn. Yet when one spends a few years studying the processes by which residents are selected and trained, the impression grows that a great deal more is involved than just transmission of information and techniques. By means of a more or less planned intervention in a normal process of personality change, rather far-reaching modifications of the physician are made, so that he grows into a new identity. This paper is devoted to some reflections on the less obvious effects of psychiatric training, unsystematically observed in the process of carrying out a long-term research project at the Menninger School of Psychiatry.*

To understand the effects of psychiatric training, then, we must first consider what is known about personality change in the decade from 25 to 35 years. At once we find, however, that this is a time of life that has been neglected by students of normal personality development. Partly this neglect may be laid to the fact that the healthy young adult, 4 to 10 years out of college, is usually an elusive subject for psychological study; he is too busy making a living and establishing a family. But it would be a mistake to suppose that a dearth of investigations indicates that little development goes on after legal adulthood is attained.

The works of White[2] and Erikson[3] stand in refreshing contrast to this general neglect. Much of the following discussion is heavily indebted to their studies of the processes of natural growth in late adolescence and early maturity.

Both of these authors emphasize the facts that maturation is a slower and more protracted process than often assumed, that it involves many trends, some of which may stand still, or even retreat, while others are advancing, and that individuals differ greatly in the speed and style of their maturing. This discussion will be organized initially in terms of four such trends.

1. The Deepening of Interests

One of the main concomitants of natural growth at this time of life, White tells us, is the deepening of interests.

A person may want to become a doctor for many reasons: prestige, social status, money . . . a zeal

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* In this research my partner from start to finish has been Dr. Lester Luborsky. It is impossible to say how much of what is contained here derives from our countless discussions during 11 years of collaborative work, but much of what has merit here is due to him.

to banish suffering. . . . Granted a sufficient level of ability, the crucial thing is the possibility to become more and more deeply interested in the details of the subject-matter and daily activities of medicine.[4]

To see how this principle applies in the development of a psychiatrist, we must ask first about the interests that bring a man to undertake psychiatric training. First, in the majority of the cases, he wants to be "a doctor." The physician occupies a unique place in the professions in the European-American social structure. He is not the only professional man to deal with matters of life and death, but none other has this responsibility so continuously and directly. This fact alone means that the decision to become a physician must have many repercussions in the conscious and unconscious motivational life of the aspirant.

Medicine and psychiatry offer their practitioners opportunities which, though not unique, are becoming less the rule in our society: the chance to do work which is inherently gratifying to important needs. A medical doctor may work much longer hours than many other men, but he is far more likely to find the processes of his work directly gratifying, not simply necessary drudgery to be performed in order to attain the necessaries that the pay check permits.

The physician has not only the duty but the privilege of helping other people. To bind wounds and nullify pain, to make a happy and effective life possible for the emotionally disturbed—these are among the deepest gratifications possible to men. Moreover, anyone with a thirst for knowledge, particularly knowledge about mankind, may find great gratification in any field of medicine. As one of the young sciences, psychiatry offers the elation of exploring and discovering new facts and principles, and the endless fascination of deciphering the hidden meanings of human conduct.

Most of the technical discussions of motivation for choosing medicine as a career stress unconscious, pregenital impulses, and infantile conflicts, or Oedipal strivings.† The fact is that medicine offers many opportunities for the sublimated (and temptations for the unsublimated) expression of such impulses.

Consider for a moment what an extraordinary thing it is that we have among us a class of men (and women) who may—and, in fact, must—examine living members of both sexes, not only in their outward aspects but also by peering into the most forbidden orifices and, by means of x-rays, into even the bones. These practitioners may touch any accessible organ of persons who may be almost complete strangers to them or who may be their personal friends; they may at times cut, burn, pierce, or poison with drugs any part of another person's body. They may command, forbid, and prescribe in the minutest detail the behavior of persons who are in their care, regulating almost all aspects of their lives. They may examine any normal or pathological product of the body, however much such interests are forbidden to others by the taboos of disgust and revulsion; they may inquire into the most intimate details of their patients' lives. And for the extraordinary privilege of doing all this, they are highly paid and accorded that premier position of status and prestige which in older times was reserved for the priest.

What a catalogue of temptations! To help him withstand these, the physician has his own internal standards of conduct and ethical values, the somewhat more remote pressure of his colleagues' ethical standards, and the still more remote external pressures of general public opinion and certain laws, such as those dealing with malpractice. He can be fairly certain that the great strength of his professional organization, the American Medical Association, is likely to be behind him if charges are brought that he has overstepped the bounds of ethical conduct; and he may be directly insured

† See, for example, Glauber,[5] Brill,[6] Fliess,[7] Nunberg,[8] and Róheim.[9]

against the financial hazards of malpractice suits.

Many doctors, of course, are not subjected to all the above temptations, and when a physician decides to specialize in psychiatry, he generally gives up the close contact with the human body that characterizes the general practitioner, though he comes into much deeper contact with the innermost secrets of people's lives. Any consideration of the motives that lead a man to choose psychiatry as a life work must take account of the opportunities and temptations put before medical practitioners generally. It must be mindful that medicine can have an appeal to men with (usually unconscious) desires to maim, dominate, and destroy others; voyeuristic desires to see and know all that is private about others; needs to have others dependent on them, admiring their wisdom and power and grateful for their miraculous gift of healing.[19]

But in a physician's personality, the destructive and narcissistic motives are under the sway of needs to love and protect others, at least so long as he is emotionally healthy. The asocial motives persist only rarely in unmodified (unsublimated) form, and even then are mainly repressed or warded off in other ways.

Once an infantile motive-source has been discovered, our understanding of the motivation for a type of behavior has only begun. The important question is: What does the person do with it? What defensive and adaptive structures have been developed to channel it into mature and useful activities? The number of root motives is small, but the ways in which they may become elaborated and harnessed to productive work are manifold. Following White, I propose that these processes result in a deepening of interests, which has a broader influence on maturation than just its facilitation of psychiatric work. For learning to cathect one's work fully helps concentration and the effectiveness of work. The more deeply a man cares about his work, the better he can do it and the more true gratification and self-respect he can get from the resulting achievement. The deepening of interests thus serves to focus and organize effort and to provide lasting sources of gratification.

This deepening of interests is partly a matter of *recruiting* and *neutralizing* a widening range of drives and their derivatives. A particular man may be drawn to medicine largely because of curiosity about people; initially, he may thus have a rather narrow motivational base for his occupational choice. Yet when he gets into the work itself, he soon encounters its appeal to his inhibited or unreleased warmth for his fellow man, and sees its relationship to general humanistic interests. Motivational systems not previously linked to his work are drawn in, and the stream of his interest is fed from many springs. Part of the fascination of psychiatry undoubtedly is its actual richness of relevance to important, universal types of motives and a great breadth of interests.

Not only are many motives appealed to in the process of psychiatric training, but they undergo ideally a progressive *neutralization*. Think of the "catalogue of temptations" just described. If medicine offers—or threatens—the opportunity to act on so many forbidden impulses, how can a sensitive person expose himself to such work without constant turmoil or yielding to these temptations? Some, of course, do yield or suffer, but they are a small minority. Others smother their sensitivities wholly or in part, covering them with defensive callousness, pedantic intellectualization, or other patterns of the kind seen so clearly in certain medical students. The most satisfactory solution, however, is to learn *adaptive modes of response that channel the aroused drives into productive activities*.

Learning to be firm with patients, for example, draws off aggressive drive-energy into a controlled, constructive outlet. There is a subtle but major distinction between

acting out hostility under the pretense of firmness and discharging it in neutralized form through the legitimate exercise of genuine firmness. Good training is what makes this difference (granted some capacity for sublimation to begin with). The early mistakes of residents often involve countertransference and the too-direct expression of impulses; supervisors expect this kind of error and, what is most important, *show the resident how to handle the same situation more constructively when it recurs.* Where he was too seductive in the warmth he showed patients in the beginning, he is taught an appropriate professional manner and technical devices for keeping objectivity without either turning off the warmth or letting it develop until doctor and patient alike are burnt. In this way, the drives that are recruited are kept in leash. They are given appropriate channels for indirect ("aim-inhibited") expression, which control them without the pathogenic consequences of repression or the other drastic defenses. This development of guiding structures for restrained release of impulse is what we mean by neutralization.‡

Here is one way, then, that the learning of a profession like psychiatry is a generally maturing experience. The settling-down aspect of growing up is an observable result of the development of psychic structure, which allows realistic gratification of some drives and neutralized expression of others, the infantile ones. Serenity can replace restlessness when a man's impulse life is taken care of by inner structural arrangements that permit gratification without excess and channel potentially disruptive archaic impulses into work.

In the Menninger School of Psychiatry, we observed that, along with the deepening of interests, many of the residents' specific aims concerning future specialization or setting of work underwent changes from the time they applied to the time they left. We believe, however, that the best residents came with a clearer idea of what they wanted and were more successful in attaining the aims they had by the end of training than were the poorer residents. Some evidence for greater initial single-mindedness in the men who turned out well comes from answers to a question in a form they filled out on admission: "What kinds of [psychiatric] work would you like to do?" A dozen possible work functions were listed; the men who became superior residents checked a smaller number of them than did any of the others, while the ones who later were inadequate gave the largest average number of choices, indicating more scattered and poorly formed interests.

Some of the failures in the Menninger School of Psychiatry, and some of the decisions to leave the field of psychiatry (with or without failure in school) were attributable to poor matching of the man's motives and abilities with the place he chose for training and the type of work. A striking characteristic of those who dropped out of psychiatry, both among those who were admitted and those who were not, was that they had applied to an institution that emphasized least the skills they typically wanted to develop—for example, shock therapy and other somatic treatments. They also had more unrealistic expectations about income returns. Sometimes the failures and dropouts among Menninger School of Psychiatry residents were due to inability to become interested in the most prevalent work interests of psychiatrists. Instead, they held on to the more center-of-the-road general medical interests. There was no necessary reason why a man should not come to the School with an interest in somatic treatments, neurology, or psychosomatic medicine, since those were parts of the School's curriculum and of the field of psychiatry. But it turned out that often such people had chosen these least psychological aspects of psychiatry because they could make only a halfway commitment to the field of their choice, and because of deficiencies in the

‡ Compare Hartmann[11] and Rapaport.[12] I realize that the view of neutralization offered here differs somewhat from that of Hartmann and Rapaport.

abilities that would enable them to do well in what is central in the field of psychiatry.

2. The Development of Self-Insight

It is hardly necessary to argue the point that maturation in early adulthood is helped along by the growth of self-knowledge. It is equally obvious that the psychiatric practitioner must develop insight into himself. He must not simply learn and use technical maneuvers to ward off or acceptably express his impulses; he must at the same time learn to become aware of them. Simply to learn to respond automatically to provocation in a way that protects oneself and controls the patient is not enough. Unless the psychiatrist can feel just enough of the anger that is drained off into his coping behavior to realize that the patient's behavior is calculated to enrage him, he may miss the significance of what is going on, and his next move may not be the right one.

By becoming a psychotherapist, a resident adds much to his understanding of what he is like, his own strengths and weaknesses, how he interacts with patients, and how he impresses supervisors. Just listening to patients can teach one much about oneself. The patient often says in no uncertain terms how he experiences the therapist—and the patient's perceptions are not all irrational transference distortions. The Topeka residents' awareness and understanding of the interactions between themselves and their patients were helped along by the discussions with supervisors and with colleagues in "group controls," a kind of continuous case seminar. Such a training program focuses on learning about patients; yet some of the light it casts must fall upon oneself as well. Several research studies have confirmed the correspondence of insight into oneself and insight into others.[13] There is no reason to believe that the self-knowledge gained in psychiatric training affects only behavior with patients. It may make possible a more realistic and satisfactory adjustment to many other aspects of life, especially through its effect on personal relationships.

Since psychiatric training does not require an equivalent of the psychoanalytic training analysis, the treatment that many Topeka residents underwent and its broadening effects on insight are outside the scope of this paper. Yet it is relevant to mention that of the 238 residents we studied during the first five years of the Menninger School of Psychiatry, 67% sought psychotherapeutic help of some kind, including training analysis, and 22% received it during the period of residency. Yet it would be absurd to say that two out of every three residents were neurotic or psychiatrically ill in some other way. The great interest in geeting personal treatment, and the resulting acceleration of growth for quite a few, is attributable in part to the climate of psychiatric training.

3. The Development of Mature Relationships with People

Psychiatric training—particularly training in psychotherapy—contributes to the attainment of mature stature through its facilitating effect on what White calls the freeing of personal relationships from transference. He lists this as another of the constructive trends that nourish maturity:

> Under reasonably favorable circumstances, the natural growth of personality moves in the direction of human relationships that are less anxious, less defensive, less burdened by inappropriate past reactions, more friendly, more spontaneous, more warm, and more respectful. Social interaction becomes more free not only from neurotic trends but also from the impulsive inconsiderateness and egocentricity of youth. . . . The developing young adult comes to interact more fully with people, making more points of contact with them.[14]

The above is a pretty good description of the kind of changes in the relationship with the patient that psychotherapy training strives to bring about. Much of training in psychotherapy may be looked on as a highly focused attempt to speed up and deepen this natural growth trend, making use of various technical devices, notably the giving of insight into countertransference. It seems likely that training of this type often, though not invariably, ramifies into other personal relationships, too, thus contributing to general maturity.

4. The Stabilizing of Ego Identity

In listing this trend, White borrows one of Erikson's most seminal concepts.[3,15,16] Adolescence and early adulthood, according to Erikson, is a time when the young person gropes to find out who he is, how he fits in, what he belongs to, and what he is going to become. Choosing and growing into an occupational role is an important experience of this type.

Psychiatric residents have just completed a first phase in the development of an occupational identity: learning to think of themselves as physicians. A recent study [17] shows that this process begins in medical school, particularly in the later, clinical years. This tendency seems to be stimulated by contact with patients, and to some extent with nurses, especially if the other person looks on the student as a doctor. The more contact the student has with patients' actual medical problems, especially when he is able to act effectively, the more he develops a sense of being a doctor.

These findings lead us to expect that the residency experience would develop a psychiatric self-image even more quickly. For the resident begins immediately to *function* as a psychiatrist; he has a responsible staff position, for which he is paid, and he is expected to perform not just as a student but as a professional man. His patients look on him as their doctor, and their very failure frequently to distinguish between "physician" and "psychiatrist" may help along the transition. For they expect and demand psychiatric care; supervisors bring to bear their parallel expectations, too. In this respect, residency is more like internship than medical school, and the feeling of being a student is quickly replaced by an awareness of oneself as a practicing professional during that year of intensive practice.

The residents of the Menninger School of Psychiatry particularly resented anything they perceived as defining them as *students*, such as examinations. This is evidence not only that they had by and large ceased to conceive of themselves as students but that the attainment of a new professional identity was a highly prized, if insecurely held, possession.

When we compared the initial interviews and the terminal interviews that were held with our subjects, one of the most obvious differences was in the residents' attitudes regarding *what they were*. They described themselves initially as wanting to be something they labeled "a psychiatrist." At the time of leaving they talked of themselves as well on the road to being that something, conceived in a much more concrete and differentiated way. During these crucial years of training, the young psychiatrist learned in detail what psychiatrists are and do; he usually had begun to think of himself as a good diagnostician, or a man who had a flair for dealing with psychopathic youngsters, or as someone who was going to become a psychoanalyst. He knew more of his own weak spots, too; a sense of identity accrues partly from a surer knowledge of what one is *not*.

The fact that a psychiatric residency is a kind of apprenticeship has another identity-stabilizing effect. Young men who had started out unsure of themselves, unable to do anything very effective in a field to which they were attracted, found they they could understand the mysteries and master the language of a difficult intellectual discipline. More important, they had found that they could help suffering people, and already had experienced the satisfaction of seeing their influence create human welfare. The transition from the awareness that one *has ability* or *shows promise* to a sense of *valid achievement*, marks an important step in the growth of adult identity.

For the resident who has not had a period of practice but has come directly from medical school and internship, the years of residency repeat the (usually hectic) experience of the internship itself in a leisurely enough way that it can be absorbed: "At last, I am really working." Medical school often means postponing the experience of going to work—at a time when most of one's friends of high school days have settled into some kind of productive occupation and are

earning a living, the would-be physician is still a student, still in a role that is at least unconsciously a childish one. In actual fact, he may be working part time to help pay his way, but oftener than not he is at least partly dependent financially (and this often means emotionally also) on his parents or parent-substitutes. The transition from being someone whose main occupation is studying to being someone who works is a crucial one in the development of adult identity and self-respect (particularly for men). Of course, a resident is still a student in a way; he is not yet wholly on his own. The process of growing up is not complete for most residents when they finish the three years; the first years of practice will do a great deal to finish it.

Ego identity becomes more stable also through external circumstances that facilitate and guide certain internal developments. Compare the social embeddedness of the entering resident with that of the graduating one: The younger man has taken a step in a direction quite different from the ones chosen by most of his contemporaries, the friends and associates who are most like himself. Since identity in an other-directed culture is to no small degree an inner reflection of what is encountered outside, going off in an unusual direction troubles one's sense of being like others, of being "all right"—it cuts one off from the support of a group tradition. As such, it is a maturing thing to do, a move toward independence and self-realization. But an individual identity must be for most of us a successful variant of some group identity, a change rung on some traditional melody.[3] Three years of working, eating, partying, studying, and conversing with a group of other men who have taken the same road can be enormously supporting. As time went on, the Menninger residents began to feel more membership in their own group as they learned a common language of psychiatric concepts, which bore a recognizably psychoanalytic imprint. We often think of identification too much in terms of introjecting older (parent-like) models; but the formation of mature identity involves large amounts of identification with one's peers.[18] Perhaps there is a special advantage to being a part of a large student body. The role of the pioneer, the different one, is splendid but lonely. To be surrounded by other young psychiatrists is not only comforting in the short run but stabilizing in the long run. It strengthens the sense of group identity, of which Erikson speaks so convincingly; such group support is all the more important if the tradition of which one becomes a part is a new one.

The common language the residents spoke was acquired primarily from the faculty and staffs of the parent institutions (the Menninger Foundation and the Winter Veterans' Administration Hospital), who also played important parts as role models, or targets for identification. Developing a professional identity partly entails becoming like someone in the field—often a teacher, a supervisor, or a therapist. We saw numerous instances in which taking such a figure as an ideal was quite conscious. Frequently, however, the process of emulation is unwitting, and the resident may not even wholly like the person with whom he is identifying himself; in such instances, symbolic and nonfunctional aspects of the other are likely to be adopted, such as mannerisms and personal tastes. Usually, however, the identity-building process is smoother and more effective if there is little ambivalence and if the resident patterns himself after his model consciously.[3,18]

The self-esteem of the maturing young adult seems to be especially fostered by the feeling that he is part of a group that is in some valued ways extraordinary: specially selected, specially trained, destined to become a vitalizing force in a profession. The Fellows of the Menninger School of Psychiatry were constantly exposed to explicit and implicit attitudes that told them: "You are members of an elite group; you are the hope of American psychiatry." Whether this was entirely justified or not, the fact is that the alumni of the Menninger School of Psychiatry could not help but develop the feeling that this group membership meant something

a good deal more than simply having completed professional training. Inevitably, an alumni association was formed, which has met regularly at national psychiatric conventions and in Topeka, and which retains a perhaps unusual degree of loyalty from its members. The group tie serves to consolidate and extend further this aspect of professional identity formation.

Finally, besides the more or less specific effects of the residency experience in stimulating and fostering personality growth, and besides the therapy that many underwent, psychiatric residents typically go through a number of other maturing experiences. Many of the Topeka psychiatrists had just recently married; others married during residency. Becoming a father was an even commoner experience than becoming a husband, and many residents' families increased by more than one during the three years. The dearth of apartments in Topeka meant that most had to buy houses, usually their initial experience in home ownership.

By the end of the three years, then, the men who were being trained in the Menninger School of Psychiatry—like those who were going through similar training elsewhere—had experienced many influences helping (or forcing) them to grow up. At the same time, they sometimes went through changes that looked regressive to a number of observers. The problem of these attitudinal vicissitudes will be taken up in the next section.

Changes in Attitudes: Morale

In addition to the more or less expected changes discussed so far, a group of rather puzzling phenomena were observed in class after class, usually following a rather regular pattern. After the daze of the first plunge into the new situation had worn off, the new students were typically fired with eagerness and excitedly immersed themselves in their work with patients and in their courses with a glowing desire to learn. The initial enthusiastic phase, however long or short it might be, was characteristically followed by a slump (usually toward the end of the first year)—a period of vague dissatisfaction, with petty complaints expressed in a variety of ways. There might follow one or more occasions of formal protest, with signed petitions and delegations of spokesmen waiting upon the authorities. Thereafter some of the residents would subside into occasional grumblings or cynical shoulder-shrugging, while these complaints would be pushed aside by more interesting and profitable concern with the work itself in the case of others.

Was this a universal phenomenon? By no means. Some residents continued to work at a rather high pitch of enthusiasm, others more quietly and steadily, without developing any particular negative feelings. Discontented students are always more conspicuous than their satisfied peers. We have no relevant statistics, but the recurrent phenomenon of the loss of "the glow" seems widespread enough to deserve special consideration.§

There were enough realistic problems inherent in the situation that the residents did not have to look far for something to complain about. There were inevitable growing pains during the first year or two of the School's existence, such as the postwar housing shortage, initial uncertainties about how and when residents would be paid, the disappointment of many residents that there was not more individual supervision, and the rebellion of others against "spoon-feeding," the feeling of some men that they were lost in the crowd of so many residents, and so forth. The fact that only a small proportion of residents could be taken into training in the Topeka Institute for Psychoanalysis created a great deal of competition and disappointment in the early classes. Though a similar problem existed in other psychoanalytic training centers, Topeka had a higher ratio of qualified and interested psychiatrists-in-training to training analysts than any other institution. (In 1946, the

§ This phenomenon as it is manifested among divinity students is described in a recent article (Shoemaker[19]), and by Heath as he saw it at Princeton in a study of undergraduate students.[20]

Topeka Institute for Psychoanalysis had only two training analysts; not until 1949 did the number reach five, though it continued to rise thereafter.) Then, overlooking the fact that the Menninger Foundation and the Veterans' Administration (not to mention several other government institutions) were making a great financial investment in them, far beyond the value of their own contributions, many residents complained that there was not more training aimed at the specific problems of private practice. This is enough of a sample to give the flavor of the specific complaints voiced by residents.

Some Interpretations of Morale Problems

To a degree, the residents' complaints were realistically justified, but they also seemed to contain an element of emotional exaggeration. One is forced to see the latter element by reflecting on the fact that the diminution of the very practical problems that afflicted residents in the early days (for example, the grave uncertainties about money and the lack of communication from the School on how their work was rated) did not result in a corresponding lessening of slumps in morale in later classes.

During the years of our project, there was a good deal of speculation about morale problems, both faculty and students trying to formulate hypotheses. A few of the latter had had residencies in other specialties, and many more had seen residents in the hospitals where they interned who in general had slightly more reponsibility than they were given in the Menninger School of Psychiatry. Moreover, the responsibility they had to take in Winter Hospital usually differed from their expectations in kind (being administrative rather than clinical), as well as in amount. Some of the Fellows in the first class pointed to the fact that they had just come from years of military service in an authoritarian structure, which most of them hated but within which they could not protest freely. Some of them felt that the griping that was so prevalent was therefore mainly blowing off steam. However true this may have been for the first class or so, it could not have applied literally to later ones. As early as July, 1946, the School had already begun to admit some men directly from internships, and very shortly they made up the greater part of the new classes. Many of them, however, had been attending school practically all their lives and were expecting to find for the first time a freer learning experience. Naturally, they were younger than the first residents had been, and by contrast many seemed callow and immature.

There was a strong tendency on the part of the faculty, therefore, to believe that what was to the residents a problem of morale was best looked on as the final throes of adolescent revolt against any and all authority. When protests were made, some of the authorities assumed that the causes were to be sought within the personalities of the residents or that the residents' unrest was simply a transference phenomenon.

There is a fairly prevalent conception that a professional man in his mid-20's is mature, or, if he is not, he should be. He is well above the average in intelligence and general ability; he has had a long and expensive education, and he has been through experiences in medical school, internship, and frequently military service in addition, which are generally thought to be "maturing." The faculty of the School, especially the administrators in the hospitals involved, often remarked in exasperation that, despite all these influences, many of the men did not *act* mature enough. A really mature person, so the argument went, would, for example, recognize that examinations might play a useful part in his own learning, as well as in the administration of the educational program; adults should not feel threatened but, rather, should only be amused if someone tries to "spoon-feed" them, something which (according to this view) happened quite rarely, anyway.

But a too ready acceptance of this explanation could lead not only to the obscuring of legitimate complaints but to a widening of the gap between the residents and their teachers. A persistent complaint of the

residents was that the faculty used authoritarian, infantilizing methods of dealing with them, instead of helping them to be adults by treating them as if they were adults. This kind of complaint led easily to the accusation that the faculty, or certain prominent members of it, were authoritarian characters, that they had "negative countertransference reactions" to the residents, and so forth. The trouble with *ad hominem* arguments, of course, is always that they can be applied to either side of a controversy without touching the manipulatable aspects of the situation, through which some progress may be sought.

Our impression is that there was some truth on both sides. To a degree, the residents *were* immature; to a degree, the School did keep them that way. The Menninger School of Psychiatry demanded and rewarded a combination of submission, rebellion, true independence of thought, and conformity to a general pattern. It simultaneously expected people to be adult—as almost any school must do—and in some ways treated them like children. This ambivalent mixture of external demands had its counterpart in conflicting trends in the residents: the need to grow up and the need to remain a dependent child.

Some Significant Foci of Development in Residents

Our research gave us the unusual opportunity of studying through interviews and tests, and of observing through the trained eyes of psychiatrists who reported to us, the personalities and actions of a fairly large sample of people in a significant, but least studied, decade of life. Unfortunately, the primacy of our practical objective kept us from making a systematic survey of our data from this particular point of view; I therefore can offer only some impressions.

From evidence in tests and interviews, it is striking how many physicians in the first half of their 20's are still struggling with residues of the Oedipal situation, more particularly with efforts to free themselves from emotional dependence on their parents. Perhaps if we could study men of this age group in other occupations, the findings would be similar. Sociologists tell us that the American family system is highly unusual in the roster of the world's societies in the demands it makes upon the children of the parental family to go forth and establish new families of their own. The new family is often geographically remote from the old one, and the children may be without communication or support from the parents. What we are seeing here is some of the psychological price that has to be paid for this system. Human beings need a great deal of support from each other, perhaps especially in a society whose ideology demands of them a high degree of initiative and frustration tolerance, and the steady pursuit of remote goals.

It should therefore be considered the most natural thing in the world that young adults *seem* outwardly to be grown up, because of great social pressure on them to do so, while at the same time they often harbor regressive longings for the easier, more carefree and irresponsible days of dependence on the parents. We should expect, also, to find that parents do not always let go as easily as their culture demands that they should, with the result that the child must frequently fight for his independence. In the process of doing so, it may become necessary for him unconsciously to conceive of the parent as a threateningly powerful, and perhaps even evil, figure.

Given this state of mind—the inner conflict over dependence and independence, the necessity to maintain a high degree of outward self-reliance and responsibility, and the unstable transitional state of his ego identity—there should be little wonder that the young professional person is typically shaky in his maturity and sensitive to any threat directed against it. He may be longing to transfer to his supervisors the dependent feelings that he is struggling to deny in relation to his parents, and he may be tempted to view any exercise of authority in light of his unconscious fantasy of the bad parent

from whose clutch he is trying to wrest himself.

In comparisons we made between TAT stories told by older residents at the end of the training period and stories told by men who had not yet entered the School, the themes mentioned above were strikingly more prominent in the latter group, who were on the average seven years younger. The older residents, particularly the ones who had done well in the School, gave evidence that the conflicts were reaching resolution, that their adult identity was more securely established, and that they could identify themselves more easily with figures in authority. In their stories, parental figures were more likely to be benign, understanding, and willing to release children who are ready to go out into the world. In interviews, the older doctors who had finished their psychiatric training showed in many direct and indirect ways fewer feelings of inadequacy and less defensiveness about themselves. Just as the projected portrait of parental figures changed, so also did the feelings toward their parents expressed in direct interview; residents at the end of training were more objective, less likely to fall over into either moralized justification of their parents or hostile feelings of having been maltreated by them.

Even though these trends are based on few cases and the method of tracing them lacks systematic rigor, they help us to understand some of the stormy episodes that occurred so regularly with residents in training. Less conspicuous in the eyes of administrators and educators, because they were less troublesome, were other, equally immature patterns of behavior, such as submissiveness to authority and hesitation to come out with independent thoughts and observations. Meager though our data are, they unmistakably suggest that these aspects of immaturity also subsided and gave way to more adult patterns during the years of training.

Maturing and Morale

According to the view urged here, the years of residency training should be looked on as a rather crucial period of transition, a period in which maturity only begins to be won by some persons and is being first consolidated by others. It is an exceptional man or woman, we believe, who emerges from the internship year following medical school with a sure sense of identity as an adult and a corresponding pattern of realistic emotional attitudes toward the crucial issues of authority, independence *vs.* passive-dependence, and responsibility *vs.* adolescent capriciousness.

Another aspect of this maturing process is often the disappearance of obvious enthusiasm, excitement, and zest. Too often, these heady qualities (which may do a great deal to stimulate a teacher) have an adolescent tinge, which is shown by their inappropriate intensity (in view of their slight basis in the students' acquaintance with the facts) and their unsteadiness. Paradoxically, the growth of a deep and sustaining interest in psychiatry may be accompained by external appearances that superficially look like a loss of enthusiasm and zeal.

There is another, simpler partial explanation for the loss of "the glow." When a person first starts the study of psychiatry, he is met with constant novelties and surprises; he may, indeed, discover what is almost a whole new world of experince, a new understanding of events and people. After he has been in the field awhile, these will no longer be novelties, and he should not be expected to approach them each day with starry-eyed wonder. It has often been held highly desirable to be able to approach experience continually with a fresh sensation of wonder and with never-ending discoveries of new things to be puzzled about and intrigued by; a few first-rate therapists seem to retain some of this quality. Realistically, however, one must expect a certain amount of waxing and waning in such an attribute.

"The glow" is partly something false, partly something true and good. It seems closely related to the first phase of falling in love, sharing the quality of romantic unrealism, in the flush of which many real features of the cathected object (the beloved,

the School, the profession) are not seen, or are even reversed. I suggest two reasons for this familiar but extraordinary phenomenon: (*a*) A person is faced with an opportunity for growth and need-gratification; impatient under the pressure of aroused drives, he regresses a little toward the pleasure principle, so that perception is wishfully distorted. (*b*) Transference interferes with realistic perception: The cathected images of "good" or "bad" parents (or other ideal figures) are projected onto the present object. Sooner or later, however, reality testing reasserts itself, and "the honeymoon is over"—disillusion of some degree sets in as the fantasy component in perception wanes and the realistic component waxes. The more unrealistic the initial glow, the deeper the disillusionment is likely to be, and the more the later reaction is likely to fall over toward paranoid unrealism.

But there is a less obvious counterpart to the loss of the glow of transferred love: What might be called the glower of transferred hate is lost by a similar process. Either way, there is a settling-down process. Even though the spice that vivid resentment gives experience is undesirable in the long run, one cannot help but feel some pang of nostalgia for the turbulence of positive and negative transferences after they have been supplanted by a more mature placidity.

Finally, on the level of realistic considerations, the psychiatric art is an extremely difficult one, much more difficult than most residents realized when they entered training. The discovery, when they began working with psychiatric patients, that, despite years of arduous study and training in medical school and internship, they were almost wholly unequipped to deal effectively with a good many of their new patients was very distressing, even depressing. One resident put it very well: "When I first started to work, it had a sobering effect on me when I saw that—dealing with patients—I could open my mouth and put my foot in it, and that psychiatric aides knew better than I how to relate to the patients. I had just been through five years of long, hard medical training, but in this type of residency I couldn't even lean on my stethoscope. It's hard to be starting out at the bottom of the heap again. It isn't possible to get by any longer only by academic proficiency or conscientiousness." According to this explanation, it was almost inevitable that residents should begin to feel inadequate, and strike out defensively and blindly against authorities or anyone else, rather than face up squarely to their own deficiencies and the enormous amount of learning that lay ahead. Or if they did recognize their own ignorance, the result often was a demand for more help faster than it could be given, followed by disaffection.

There can be no doubt, we believe, that psychiatry *is* a subtle, complex, and personally threatening type of practice, one for which many medical schools ill prepare their graduates. This seems to us a factor that needs to be taken into account in an assessment of residents' morale problems.

Summary

A great deal happens to a man or woman during the years of psychiatric training besides the acquisition of knowledge and skill. The strains of exposure to work with psychiatric patients and their occasional pathogenicity are well known; I have tried to show how psychiatric training itself contributes to maturity through the deepening of interests, the development of self-insight, the development of sound relationships with people, and the stabilizing of ego identity. At the same time, the training process induces apparently regressive changes, seen in morale problems and the loss of the initial enthusiastic glow. These phenomena themselves may be part of growth and the attainment of a mature professional identity. They should, therefore, not be greeted with alarm or discouragement when they appear in psychiatric residents; neither should the fact that they may occur naturally lead to complacent assumptions that nothing can or need be done to improve psychiatric training.

REFERENCES

1. Holt, R. R., and Luborsky, L.: Personality Patterns of Psychiatrists, New York, Basic Books, Inc., 1958.

2. White, R. W.: Lives in Progress, New York, Dryden Press, 1952.

3. Erikson, E. H.: Childhood and Society, New York, W. W. Norton & Company, Inc., 1950.

4. White,[2] p. 351.

5. Glauber, I. P.: A Deterrent in the Study and Practice of Medicine, Psychoanalyt. Quart. 22:381-412, 1953.

6. Brill, A. A.: Basic Principles of Psychoanalysis, New York, Doubleday & Company, Inc., 1949.

7. Fliess, R.: Autopsic Encumbrance, Internat. J. Psycho-Analysis 35:8-12, 1954.

8. Numberg, H.: Practice and Theory of Psychoanalysis, Nervous and Mental Disease Monograph 74, New York, Nervous and Mental Disease Monographs, 1948.

9. Róheim, G.: War, Crime and the Covenant, New York, International Universities Press, 1945.

10. Menninger, K. A.: Psychological Factors in the Choice of Medicine as a Profession, Bull. Menninger Clin. 21:51-58, 99-106, 1957.

11. Hartmann, H.: Notes on the Theory of Sublimation, in Psychoanalytical Study of the Child, edited by R. S. Eissler, 1955, Vol. 10, pp. 9-29.

12. Rapaport, D., Editor: Organization and Pathology of Thought: Selected Sources, Austen Riggs Foundation Monograph No. 1, New York, Columbia University Press, 1951.

13. Dymond, R. F.: The Relation of Insight and Empathy, J. Consult. Psychol. 12:228-233, 1947.

14. White,[2] p. 343.

15. Erikson, E. H.: On the Sense of Inner Identity, in Health and Human Relations, Conference on Health and Human Relations in Germany, New York, Blakiston Company (Division of McGraw-Hill Book Company, Inc.), 1953.

16. Erikson, E. H.: The Problems of Ego Indentity, J. Am. Psychoanalyt. A. 4:56-121, 1956.

17. Huntington, M. J.: The Development of a Professional Self-Image Among Medical Students, in The Student-Physician: Introductory Studies in the Sociology of Medical Education, edited by R. K. Merton, P. L. Kendall, and G. G. Reader, Cambridge, Mass., Harvard University Press, 1957.

18. Howe, L. P.: Identification: A Psychoanalytic and Sociological Essay, to be published.

19. Shoemaker, S. M.: Where Goes the "Glow," Christian Cent. 70:508-509, 517, 1953.

20. Heath, S. R.: Student "Characters," Princeton Alumni Week. 56:8-11 (13), 1956.

Water-Loading Test in Mental Diseases

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Water metabolism in mental diseases is an interesting problem. Earlier findings have been summarized by Altschule[1] in 1953. He recalled the widely divergent factors complicating this matter. Emotional experiences have a profound influence on water metabolism.[2] Both emotional and physical stimuli can inhibit diuresis by releasing antidiuretic hormone.[3,4] The Worcester group has described abnormalities of the water metabolism in schizophrenia. According to their findings,[5] the urinary excretion of water is increased in the resting and fasting schizophrenic. For some time now the role of the hypothalamus in mental diseases has aroused the interest of the profession.[6] Unfortunately, the activity of many hypothalamic centers defies quantitative measurement. It is in this connection that here an effort has been made to follow the activity of organs involved in water diuresis in mental diseases. In spite of complicating factors, here is something that can be measured and weighed.

Methods and Material

The patient abstained from food and water after midnight. At 6 a. m. he voided; specific gravity and volume of the night specimen were noted. He then drank 1,000 cc. of water.

1. Inactive Test: Patient remained in bed except for voiding every 30 minutes for 3 hours; specific gravity and volume were noted
2. Active Test: Same as Test 1 except that the patient sat up
3. Cortisone Test: Same as Test 1 except that at 4 a. m. 150 mg. of cortisone was given by mouth
4. Corticotropin Test: Same as Test 1 except that at 4 a. m. 40 units of corticotropin was given intramuscularly.

Room temperature was kept at 80 F. A note was made of the patient's mood and reactions.

Care was taken to exclude patients with complications that might interfere with diuresis, such as renal or circulatory disabilities. Alcoholics were not tested until acute symptoms had subsided. Patients with liver damage were excluded. If mental deterioration had occurred, they were grouped under the "organic" alcoholics. When alcoholism was associated with pronounced functional symptoms, the patients were grouped under the "functional" alcoholics; the rest were considered as "normal" alcoholics.

All patients with "functional" psychoses had to be able to cooperate; severely disturbed patients were excluded.

Complicating factors cannot be disregarded. The second group in our Table, the "active" one, demonstrates how much even limited activity inhibits diuresis. But the activity in the "inactive" (first) group cannot be entirely controlled. Even the amount of turning in the bed must interfere with the results to a certain extent. A major error can develop if the environmental temperature is not controlled. An elevation beyond 70 F diverts increasing amounts of excretion from the kidneys to the lungs and skin. We have made an effort to keep the room temperature at 80 F. Specific gravity moves opposite to the volume and allows a control of the consistency of results.

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Water-Loading Tests in Mental Diseases

	Inactive			Active			Cortisone (150 Mg.)				Corticotropin (Units)					
											40 W			80 N		
	No. of Cases	Mean Excretion	Standard Deviation	No. of Cases	Mean Excretion	Standard Deviation	No. of Cases	Mean Excretion	Diff. of 1st & 3d	Standard Deviation	No. of Cases	Mean Excretion	Standard Deviation	No. of Cases	Mean Excretion	Standard Deviation
Alcoholism																
"Normal"	24	811	279	24	589	254	19	1,094	+283	307	8	387	161	4	847	180
"Functional"	19	1,042	196	17	740	317	13	980	−62	210	6	375	208	3	1,076	247
"Organic"	10	827	185	10	648	334	9	1,269	+442	221	10	332	167			
Schizophrenia																
"Paranoid"	24	1,107	310	23	722	293	23	1,121	+14	310	18	352	151		1,185	120
"Hebephrenic"	10	806	241	8	605	171	7	949	+53	125	6	238	161			
"Catatonic"	6	933	200	6	631	305	6	961	+28	165	4	398	215			
"Simple"	9	952	208	8	676	272	8	806	−56	164	3	418	270			
After insulin	22	802	229				22	980	+127	257						
Involutional	14	951	245	15	526	225	14	1,055	+104	296						
Encephalopathy	8	1,092	484	8	825	320	8	1,335	+243	393	3	375	198	4	1,208	392

It is well established that emotional stimuli reduce the renal excretion of water. No such stimuli were introduced externally in our material, and it is thought that the results largely reflect the internal milieu. Here the assumption is made that endogenous mood swings reflect the internal milieu also and, therefore, will not vitiate the results. Even so, the rather large standard deviations reveal the variability inherent in the method. We consider our results only as clinical trends. However, controls with great number of cases, as might be available in state hospitals or chronic-type neuropsychiatry institutions, may well result in statistically valuable information.

That the adrenal cortical hormones are able to stimulate diuresis in the acute experiment has been known for some time.[7] This is probably a consequence of their ability to inhibit reabsorption of water in the tubules. Their diuretic strength is demonstrated in our third group (cortisone test). Originally it was planned to use this additional diuresis in order to test the ability of the adrenals to secrete cortisone in response to corticotropin. Group 4 however, reveals that corticotropin W must contain vasopressin U. S. P. (Pitressin) because invariably it resulted in inhibition of diuresis. Corticotropin N was found free from vasopressin, and its administration resulted in values comparable with those for the cortisone group. There was no case of adrenal insufficiency in our material.

In all, 477 tests are summarized in the Table.

Results

The Table reports the number of cases, the mean output, and the standard deviation. The first group is concerned with the inactive, and the second with the active, state; the third, with the response to cortisone, and the fourth and fifth, with the reaction to corticotropin. In Group 3, an additional report is made on the difference between the mean output of Groups 1 and 3. This records the ability of the patient to respond

to cortisone with additional diuresis in excess of the resting state.

The "normal" alcoholic showed an adequate response to water loading in the inactive test. The cortisone test revealed their strong ability to respond to cortisone stimulation with additional diuresis of 283 cc. The difference between this group and the paranoid schizophrenia group was obvious. There was larger excretion of urinary water in the inactive schizophrenic patient; at the same time, the schizophrenic in the third group seemed unable to respond to stimulation with cortisone. Most of the schizophrenics were comparable in this respect. Interestingly, the "functional" alcoholics, a group that combines alcoholism with functional symptoms, reacted very much like the schizophrenic, with a high output on the inactive test and a lack of response to cortisone. There was little difference between the "normal" and the "organic" alcoholic, although possibly in the "organic" type a weakness in output of antidiuretic hormone could be suspected as a cause of the ready response to cortisone.

It has been mentioned that the resting schizophrenic put out an unusually large amount of urine under water loading, and that he failed to respond to cortisone stimulation with increased diuresis. In our material, insulin treatment has been able to reverse the situation, decreasing output in the inactive test and increasing it under cortisone stimulation.

In a few cases of "functional" neuroses not reported here in detail the reaction was comparable to that in schizophrenia. This is in contrast with our involutional psychosis patients, who have been able to respond to cortisone.

Some organic cases seem to lack adequate response of the antidiuretic hormone center, as though these centers had undergone some damage. These cases, however, responded readily to cortisone (encephalopathies).

Summary

The results in 477 water-loading tests in mental diseases are reported.

"Normal" alcoholics increase their urinary output of water in the water-loading test when stimulated by cortisone.

The fasting and resting schizophrenic shows an increased diuresis in 1,000 cc. water-loading test, but is unable to increase the diuresis under stimulation with cortisone, as the normal subject does.

Insulin treatment is able to reverse this picture to normal.

"Functional" neurotics react comparably to the schizophrenic in the water-loading test.

In some organic cases (encephalopathies) a weakness of the antidiuretic hormone centers is revealed, resulting in increased diuresis. These cases respond to cortisone with further increase of diuresis.

The variability inherent in the test reserves for it only suggestive value in any diagnostic problem.

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REFERENCES

1. Altschule, M. D.: Bodily Physiology in Mental and Emotional Disorders, New York, Grune & Stratton, Inc., 1953.

2. Schottstaedt, W. W.; Grace, W. J., and Wolff, H. G.: Life Situations, Behaviour, Attitudes, Emotions, and Renal Excretion of Fluid and Electrolytes: V. Variations in Excretion of Endogenous Creatinine, J. Psychosom. Res. 1:292-298 (Nov.) 1956.

3. Mirsky, I.: A Secretion of Antidiuretic Hormone in Response to Noxious Stimuli, A. M. A. Arch. Neurol. & Psychiat. 73:135-137 (Feb.) 1955.

4. Verney, E. B.: Croonian Lecture: Antidiuretic Hormone and Factors Which Determine Its Release, Proc. Roy. Soc., London s. B. 135: 25-106 (Dec. 16) 1947.

5. Hoagland, H.; Bergen, J. R.; Slocombe, A. G., and Hunt, C. A.: Studies of Adrenocortical Physiology in Relation to the Nervous System, A. Res. Nerv. & Ment. Dis., Proc. (1952) 32:40-59, 1953.

6. Gellhorn, E.: Physiological Foundation of Neurology and Psychiatry, Minneapolis, University of Minnesota Press, 1953.

7. Gaunt, R., and Birnie, J. H.: Hormones and Body Water, Publication No. 103, American Lecture Series, edited by R. F. Pitts, Springfield, Ill., Charles C Thomas, Publisher, 1951.

Effect of Two Psychological Stresses on Adrenocortical Function

Studies on Anxious and Normal Subjects

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In a previous publication [1] it was reported that the disturbing experience of being introduced into a strange and potentially dangerous place or of being subjected to an anxiety-evoking psychiatric interview raised the plasma level of the adrenal cortical hormone, hydrocortisone, in a group of anxious patients 40% and 28%, respectively. The increase in hormone level following the interview was also associated with a significant increase in emotional responses.[2] The present study is intended to extend the earlier work in two directions: to investigate response to another type of psychological stimulus and to make a comparison of normal subjects and psychiatric patients, which was not possible in the earlier experiment. We shall here compare the response of two groups differing considerably in anxiety-proneness to the same situation, and also two groups of the same (high) level of anxiety in response to two different stress procedures.

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The experimental condition used in the present study involves the manipulation of a perceptual judgment task in such a way as to produce an experience of perceptual distortion. Compared with the interview situation, the focus is upon the relationship between the patient and external events more than upon the relationship of ego factors to internal attitudes or needs. In both cases, however, the effort is made to evoke anxiety by implying a failure of ego control.

Subjects, Experimental Design, and Methods

The anxious patient group of the present study consisted of 11 hospitalized patients (7 men and 4 women), with a mean age of 39.8 years. These patients were all hospitalized on the psychiatric service of a general hospital at the time of the experiment and were selected to resemble the 19 anxiety-prone patients of the earlier study as closely as possible.[3] Five male soldiers, with an average age of 22.4 years, comprised the normal subject group. These men were selected from a larger group of volunteers on the basis of a diagnostic interview finding them relatively free of anxiety or psychological disturbance. In later discussion, the patient group subjected to the interview procedure in the earlier experiment will be called Group API; the patient group subjected to perceptual distortion in the present study, Group APP, and the normal soldier group, tested under the same condition, Group NSP.

All subjects of the present study (Groups APP and NSP) were in good physical health, as judged by physical examination. No medication was administered for either group during the experimental sessions, although some of the patients received sedative or tranquilizing drugs at night between sessions, usually in low dosage. It is not

believed that the age and sex differences between the two groups of subjects can account for the differences to be reported in adrenal cortical function. Previous unpublished studies in this laboratory indicate no significant differences in plasma hydrocortisone level, plasma hydrocortisone response to corticotropin, or urinary excretion of hydroxycorticoids between subjects whose mean age is 20 years and another group aged 40, or between men and women at each of these age levels.

The experimental setting, laboratory conditions, scheduling, and, in general, the nature of the procedures employed in the present study were in most respects identical with those used in the previous study[3] except with regard to the experimental condition interposed between the *pre* and *post* blood samples.

In both cases, the experimental design consisted of four consecutive days. The first of these was a "preexperimental day" on which the various measurements were made but no explicit stimulus introduced. On the three successive days, which will be referred to as Days 1, 2, and 3, a series of measurements was repeated, first, before and, then, after the experimental condition. For our present purposes, it should simply be noted that *pre* and *post* measures of plasma hydrocortisone bracket this stress-stimulus.

The "perceptual distortion stress" consisted of one task (length estimation) repeated on each of the three experimental days, with a second task (picture description) introduced on the third day. The technique and an overview of findings obtained in this study have been described elsewhere.[4] The length-estimation task involved a series of pairs of lines, with the subject asked to judge which of the two was longer. To validate this judgment, the subject was then shown what he presumed to be the same set of lines and was asked to measure them. On selected occasions during the validational phase, however, an alternate pair of lines was surreptitiously introduced, so that the subject was given the impression that he had erred in his judgment. The position of the lines, and other characteristics of the stimulus, were sufficiently similar that the deception was not discovered by any subject. On the third day the subject was also shown a series of photographs, in this case rapidly exposed (0.25 second), and asked to describe what he saw. After each judgment, he was shown what he believed to be the same photograph and asked again to describe it, this time with the picture in full view and with unlimited time available. However, in every case the subject was shown an altered version on the second viewing. The pairs were so constructed that the first usually contained some threatening content, for example, suicide, hostility, death, etc., and the alternate version was distinctly more neutral. Thus, the originally presented member of the first pair showed a man bent over, appearing somewhat depressed, with a gun to his temple. The alternate version, shown immediately after, presumably so that the subject could check the accuracy of his earlier judgment, showed the man in much the same position, looking thoughtful, and, most important, holding a pipe rather than a gun to his temple. The implication, then, is that the subject had projectively perceived a scene of self-destruction, when in fact there was no reality basis for this judgment.

The number of errors imputed to the subject in the length-estimation task was increased each day, and, as noted, the picture-description task was added on the third experimental day. Consequently, the intention was that the intensity of stress-stimulus be increased from day to day. Moreover, the quality of the stimulus was somewhat altered on the third day, since it was implied not only that the subject was not accurate in his judgment but, in addition, that he was projecting into a presumably objective description of an external stimulus his own inner needs and neurotic conflicts. Taken together, however, the two parts of the perceptual distortion procedure imply an inadequacy of perceptual functioning, hence a failure of ego control, and thus mentally unhealthy behavior.

The plasma level of hydrocortisone was determined according to Nelson and Samuels,[6,7] and the urinary hydroxycorticoids, by a modification[3] of the method of Reddy.[8] All urine samples were checked for completeness of collection by means of a determination of their creatinine contents.[9] The ratings for anxiety, anger, and depression were made in exactly the same way as in the earlier studies and have already been described in detail elsewhere.[2,10]

Results

Effect of Two Different Psychological Stresses on Adrenocortical Function in Two Groups of Anxious Patients.—When the mean plasma levels of hydrocortisone in anxious patients disturbed by means of the perceptual distortion situation are compared with those of anxious patients stimulated by means of a disturbing interview, no significant difference occurs on any of the 12 occasions (Table 1). Further, the two groups do not differ significantly on any of the four days in the *change* in level from the pre measures to the post measures (Table 2). However, it is interesting that Group AP1 is more variable in its hydro-

TABLE 1.—*Plasma Hydrocortisone Level of Anxious Patients and Normal Subjects in Three Stress Experiments*

Occasion	Plasma Hydrocortisone Level, μg. % *			t †	
	API	APP	NSP	API *vs.* APP	APP *vs.* NSP
Preexperimental day					
Pre (9:00 a.m.)	19.5±6.6	20.6±8.6	10.9±7.9	0.37	5.18 [3]
Post (10:30 a.m.)	19.6±6.8	18.7±8.8	8.9±4.3	0.30	2.81 [1]
Extra (2:30 p.m.)	15.1±5.3	10.8±5.9	4.9±1.1	1.92	2.92 [1]
Day 1: Pre	21.7±7.3	20.4±7.9	11.8±2.8	0.44	2.92 [1]
Post	15.6±5.1	14.0±9.0	11.4±4.0	0.59	0.75
Extra	12.1±4.7	14.2±4.5	7.7±4.7	1.08	6.20 [3]
Day 2: Pre	18.1±6.6	21.2±7.6	8.5±2.8	1.09	4.50 [3]
Post	14.8±7.3	14.6±5.7	10.9±6.6	0.08	2.64 [1]
Extra	12.8±5.6	12.8±5.9	7.3±6.0	0.02	3.66 [3]
Day 3: Pre	19.3±5.9	16.9±6.2	13.1±2.6	0.96	1.59
Post	13.3±6.7	12.2±8.6	10.0±4.8	0.37	0.61
Extra	11.3±4.9	13.6±7.2	5.9±7.0	0.99	4.77 [3]

* Mean (±) standard deviation; 18 subjects in Group API, 9 in Group APP, and 5 in Group NSP, for whom complete data were obtained.

† Appropriate methods for the comparison of the levels were employed when the variance was nonhomogeneous. For the API *vs.* APP comparison, a value of 2.06 is necessary for the 5% level of significance; for the APP *vs.* NSP comparison, a value of 2.18 is necessary. The numeral 1 (superior) means that the value is significant at better than the 5% level; 2, at the 1% level; and, 3, at the 0.1% level.

cortisone change values on each of the three experimental days, although initially (on the preexperimental day) it is the less variable group; yet in all comparisons the variance ratios are short of statistical significance. Hence, it would seem that, while there is no important difference in the *extent* of response, the interview tended to have more individualized effects than the perceptual procedure.

Since some diurnal fall is expected, measures of change taken from an earlier to a later time might be corrected for expected diurnal variation.[1] But since the correction would be identical for both these groups, any tests of differences between them would not be affected. Thus, the two patient groups show no difference either in the levels or in the degree of response to the two experimental conditions. The urinary output of hydroxycorticoids, a group of metabolic products derived from hydrocortisone, also did not differ significantly on any of the experimental days (Table 3).

The ratings of affects, corresponding to the time of hydrocortisone measure, for the two anxious groups show essentially similar increases in emotional response as a function of both the interview and the perceptual conditions (Table 4). Only on the second experimental day, which we have noted elsewhere[1] to be a particularly disturbing day

TABLE 2.—*Change in Level* (Post *Minus* Pre) *of Plasma Hydrocortisone of Anxious Patients and Normal Subjects in Three Stress Experiments*

Occasion	Change in Plasma Hydrocortisone Level, μg. % *			t †	
	API	APP	NSP	API *vs.* APP	APP *vs.* NSP
Preexperimental day	0.11±7.52	1.89±12.20	−2.00±10.56	0.53	0.04
Day 1	−6.14±7.12	−6.39±6.16	−0.48±2.10	0.09	2.30 [1]
Day 2	−3.29±10.00	−6.58±5.71	−2.42±5.88	0.91	1.97
Day 3	−5.99±8.20	−4.74±7.02	3.14±4.84	0.39	0.34

* Mean (±) standard deviation.

† Appropriate methods for the comparison of the change scores were employed when the variance was nonhomogeneous. Numeral 1 (superior figure) means that the value is significant at better than the 5% level.

TABLE 3.—*Urinary Hydroxycorticoid Excretion of Anxious Patients and Normal Subjects in Three Stress Experiments*

Occasion	Urinary Hydroxycorticoid Excretion, Mg/Day *			*t* †	
	API	APP	NSP	API *vs.* APP	APP *vs.* NSP
Preexperimental day	8.20±4.92	9.61±4.03	5.28±2.25	0.80	2.58 [1]
Day 1	8.23±7.12	10.09±6.03	4.72±2.42	0.73	2.35 [1]
Day 2	6.20±5.54	9.68±4.38	4.54±4.56	1.77	5.05 [3]
Day 3	7.92±7.74	9.03±5.63	4.68±3.05	0.41	1.88

* Mean (±) standard deviation; 18 subjects in Group API, 11 in Group APP, and 5 in Group NSP, for whom complete data were obtained.

† Appropriate methods for the comparison of levels were employed when the variance was nonhomogeneous. Superior numerals indicates that the value is significant at better than the 5% level; superior figure 3, that it is significant at the 0.1% level.

for the interview group, did Group API show any more response in anxiety, and this difference is significant at the 0.05 level. It can also be noted that the largest increment of plasma hydrocortisone also occurred on the second day for this group.

In an earlier report [2] it was shown that when the three interview days were ranked for each individual according to days of greatest, median, and least emotional response for each of the affects separately and for the combined rating, there was a regular and significant change in hydrocortisone response from day of greatest to day of least affective change. A similar analysis done for the subjects of the perceptual experiment shows more consistency of emotional response, and, consequently, less difference when subjects are ranked on days of highest, median, and lowest emotional response. Since there is less range along this dimension, it is not surprising that the hydrocortisone response tends to be more similar on each of the three days than in the first experiment.

Effect of the Perceptual Stress Technique on Adrenocortical Function of Two Groups of Subjects Differing in Anxiety.—The comparison of normal subjects (Group NSP) and anxious patients (Group APP), subjected to the same perceptual distortion situation, shows the plasma hydrocortisone level of the anxious patients to be clearly higher, on the average about 80% above, than that of the normal subjects when they are compared occasion by occasion (Table 1). On 9 of these 12 occasions, the difference is clearly significant; in no case is there an instance of reversal. The amount of difference reported here is roughly similar to that previously reported for comparable groups.[1,11,12]

While the two experimental groups show roughly the same amount of change, from *pre* to *post* measurement on the preexperimental day, the normals respond relatively more (i. e., have less diurnal fall) on each of the experimental days, with the difference between the two groups in the amount of response achieving the 0.05 level on Day 1 and falling just short of this level on Day 2 (Table 2). From these data, therefore, one might conclude that the preexperimental day, with its uncertainties and unknown dangers, constituted the greatest disturbance for the patient group, while, by comparison, the normal subjects were more stimulated by the intended experimental conditions. The sensitivity of anxious patients to the preexperimental day has already been noted in the Group API subjects in the interview experiment.[1,13]

It is known that hydrocortisone levels fall during the course of a morning. Such effects as the experimental conditions might have are therefore superimposed upon an expected diurnal cycle. Various methods can be used to correct for this phenomenon, thus making possible an estimate of induced change uncontaminated by indigenously determined changes. We have employed a method involving the subtraction of an average correction factor based on the obtained mean changes of subjects tested at equivalent

TABLE 4.—*Change in Affect* (Post *Minus* Pre) *of Anxious Patients in Two Stress Experiments*

	Change in Affect *											
	Anxiety			Anger			Depression			Combined Affect		
Group	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
APT	0.09±0.75	0.78±0.54	0.98±0.63	0.28±1.10	0.69±0.91	0.28±0.86	0.36±0.86	1.10±0.95	0.72±0.86	0.72±2.12	2.56±1.78	1.91±2.04
APP	0.30±0.46	0.27±0.63	0.53±1.11	0.70±0.46	0.22±0.44	0.24±0.93	0.69±0.39	0.58±0.46	0.56±1.01	1.69±0.88	1.07±1.01	1.33±2.40
t	0.77	2.17	0.36	1.10	1.44	0.40	1.05	1.54	0.46	1.30	2.32	0.37
P	N. S.	<0.05	N. S.	N. S.	N. S.	N. S.	N. S.	N. S.	N. S.	N. S.	<0.05	N. S.

* These values are mean change scores and standard deviations of arbitrary ratings, whose derivation is explained more fully elsewhere. [4] Complete data were obtained for 17 subjects in the APT group and for 9 subjects in the APP group.

times under the most "basal" conditions feasible in a hospital.[1] To obtain these correction values, 8 anxious patients and 12 normal subjects were tested at 9:00 and 10:30 a. m. The patients had a mean 9:00 a. m. value of 21.7±9.5 and a mean 10:30 a. m. value of 14.2±7.0; the normals had corresponding means of 9.9±5.5 and 7.5±5.6. The average change scores (9:00 a. m. minus 10:30 a. m.) values of 7.6±6.8 for the patients and 2.4±6.7 for the normals can serve as approximations of the expected change for each of our present groups. Subtracting these values from the obtained 9:00 a. m. level yields an expected 10:30 a. m. value, and the difference between this and the obtained 10:30 a. m. value can then be taken as an index of stress response. Should the obtained value be higher than the expected value, it might be said that the experimental condition raised hydrocortisone levels.

The mean change scores based on this method of adjustment are given in Table 5. While the patients show some degree of response on each of the four days of the experiment, the greatest amount is on the preexperimental day. By contrast, for the normals the adjusted change scores on the preexperimental day and the third experimental day are close to zero, i. e., almost identical with the control normal subjects,

TABLE 5.—*Change in Level* (Post *Minus* Pre) *of Plasma Hydrocortisone, Adjusted for Expected Diurnal Change, of Anxious Patients and Normal Subjects in a Perceptual Distortion Stress Experiment*

Occasion	Change in Plasma Hydrocortisone Level, μg. %. *		
	Anxious Patients	Normal Subjects	t †
Preexperimental day	5.7±12.2	0.4±10.6	0.81
Day 1	1.2±6.2	1.9±9.2	0.25
Day 2	1.0±5.7	4.8±5.9	1.18
Day 3	2.9±7.0	−0.7±4.8	1.01

* Mean (±) standard deviation for nine anxious and five normal subjects.

† This value was calculated by the appropriate methods used when the variance was nonhomogeneous. A value of 2.18 is necessary for the 5% level of significance.

and what effects exist are to be found on the first and, particularly, the second experimental day. However, none of the comparisons between days within each of the groups shows these differences to be statistically different, nor, as is shown in Table 5, are any of the comparisons between groups in the values for matched occasions significant. Lastly, there are no significant differences between the adjusted change values of either group on any of the four days and the obtained change values of the appropriate control groups. Stated in another way, the values given in Table 5, in the effort to abstract stress response, are not significantly different from what might have been expected had these same subjects been studied under more nearly basal conditions. Consequently, it can be concluded from this analysis that the apparent stress effects are at best small, and do not differ importantly between occasions or groups.

We are quite uncertain whether this mode of adjustment, or any other, is justified, or whether the initial presentation in terms of raw scores gives a better picture of the results of this experiment. It is a serious question whether the same constant should be applied to all subjects within the same group, or whether the expected change should not vary with the initial level. There is evidence that the amount of diurnal change, in terms both of direction and of extent, might be dependent upon the starting level of hydrocortisone production. It should also be noted that the reference groups used were quite small and that the mean "constants" yielded by them involve considerable amounts of variance. The analysis is presented here to illustrate an alternate way of viewing the data of this experiment, and to indicate the uncertainty in their interpretation.

The urinary excretion of hydroxycorticoids of the anxious patients is significantly higher than the normals on every occasion of testing, though the confidence level does not quite reach 0.05 on the third experimental day (Table 3). The daily urinary output of the patients runs about 100% above that of the normal subjects, the same order of difference reported previously in similar comparisons.[1,11,12]

The distinct differences between the normal and the anxious subjects in plasma hydrocortisone level and in urinary hydroxycorticoid excretion are paralleled by wide differences in the affective ratings of the two groups. On each of the paired occasions, the patients were significantly higher in anxiety, anger, and depression ratings, and in the total emotional arousal represented in a composite rating, although the amount of change from before to after the perceptual procedure was roughly comparable in the two groups. Consequently, as we have discussed elsewhere in greater detail,[4] the patients both enter the experiment and respond to participation in it with over-all higher levels of affective arousal, although the stimulus proper does not evoke any greater amount of additional response.

Comment

This study was undertaken with two questions in mind: 1. Do different types of psychological conditions produce different responses in essentially similar subjects? 2. To what extent do subjects, initially quite dissimilar in anxiety, respond differently to the same, standardized condition?

It is clear from the material presented that the differences between the groups of anxious patients subjected to the interview and perceptual distortion conditions are small and, in the main, insignificant. Mean plasma hydrocortisone level and change in level, urinary output of hydroxycorticoids, affect levels, and change in levels (with some exceptions) did not differ significantly between the two groups. Consequently, the anxious patients confronted by two rather different procedures respond in essentially the same way, at least in terms of these general indices of emotional and hormonal stress response. There are, of course, many specific differences in behavior in the two situations, some of which have been discussed

elsewhere,[1] but these are not reflected in the present analyses.

In both cases, the patients approached the experimental situations with a considerable degree of anticipatory anxiety. There were heightened fears of the unknown situation and the laboratory and its complicated and awesome equipment. Over-all, there must have been a genuine concern with the meaning of the "tests" and the possibility that the findings would bear on their course in the hospital. Consequently, the highest levels of disturbance were reached prior to and early in the series of experimental days. Against this background, the intended stimulation produced rather little change in adrenocortical functioning—the largest response having appeared on the first day in the laboratory—although there were regular rises in emotional levels in response to each day's experimental condition. In this respect, both groups of patients differ from the normal soldiers, who show distinctly less general, and somewhat more focal, stress response.

Although it was originally intended, in both studies, to increase the intensity of disturbance from day to day, in neither case was it really possible. The maximum response to the interview was on the second experimental day; with the perceptual procedure the responses were more uniform on the three days, although the normals did have relatively greater affective responses on each day. In one regard, however, the perceptual distortion condition seems to have more predictable effects. There is generally less variability in adrenocortical response on each of the experimental days within Group API than within Group API, though the difference is well short of statistical significance. Paralleling this, the range of emotional response, when the experimental days for each subject are viewed separately, is greater in the interview study. Stated otherwise, the subjects in the interview study tend to be more disturbed on their day of greatest emotional arousal, and less disturbed on the day of least arousal, than the patients in the perceptual distortion experiment. Consequently, while it was found that the degree of adrenocortical change was significantly different on days grouped in terms of affective arousal in Group API, such a relationship was not found in the second experiment, probably because of the smaller range of affective changes.

Normals and patients, to comment on the second question raised, differ clearly in one major respect. Plasma hormone level and urinary hydroxycorticoid output, along with affect level, are significantly different at the outset and throughout the experiment, as indeed has been reported in other comparisons of similar groups. These indices are clearly related to difference in chronic disturbance level, and the difference is not altered greatly by the specific events of the experiment. However, what is more interesting is evidence of somewhat greater stress *response* in the normals. Both groups show about the same absolute rise in levels, but since this change is against a lower base for the patients, it might even be argued that they had proportionately more affective response. We have seen, however, that the hormonal response is generally greater on the normals' stress days, though there is still question of the proper way of interpreting differences in degree of change between two groups differing markedly in level. It might also be true that the patients' lower hormone increase may simply reflect the fact that this group is operating at near-maximal levels and that further increase is physically impossible.[12] An additional possibility is that the normals experienced the intended disturbances more acutely. Unlike the patients, they arrived in the laboratory relatively free of apprehension, nor were they visibly troubled by the novel experiences of the laboratory on the preexperimental day. Against this benign expectation, the perceptual failure quite probably stood out sharply, as unexpected and inexplicable insult. While the patients brought with them a history of failure and were absorbed with their larger life problems—additional stimulation there-

fore not adding importantly—the normals had no reason to believe that they could not handle adequately the apparently simple perceptual tasks. Consequently, their ordinarily fairly high self-esteem could be threatened more readily by the circumscribed failure experience. Simply coming into the laboratory and participating in the experiment is for the more disturbed subject the greatest threat, as we have discussed before,[4,13] since the unknown, and hence fantasied, dangers seem greater than we were able to produce experimentally.

Summary

Two groups of anxiety-prone psychiatric patients were subjected to two different psychological techniques: an anxiety-evoking interview and a judgmental situation which suggested that the subject's perception was distorted. The plasma hydrocortisone level, urinary hydroxycorticoid output, and affect ratings for anxiety, anger, and depression did not differ significantly for the two groups. The anxious patients reacted to the preexperimental day with a greater plasma hormone response than on any of the experimental days. A group of normal subjects were significantly lower than patients in plasma hydrocortisone level, urinary hydroxycorticoid output, and affect rating. By contrast, the normal subjects reacted more vigorously to the intended experimental stress.

Miss Betty Lou Day gave technical assistance, and Dr. Helen Heath, help with the statistical analyses.

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REFERENCES

1. Persky, H.; Grinker, R. R.; Hamburg, D. A.; Sabshin, M. A.; Korchin, S. J.; Basowitz, H., and Chevalier, J. A.: Adrenal Cortical Function in Anxious Human Subjects: Plasma Level and Urinary Excretion of Hydrocortisone, A. M. A. Arch. Neurol. & Psychiat. 76:549, 1956.

2. Persky, H.; Hamburg, D. A.; Basowitz, H.; Grinker, R. R.; Sabshin, M.; Korchin, S. J.; Herz, M.; Board, F. A., and Heath, H. A.: Relation of Emotional Responses and Changes in Plasma Hydrocortisone Level After Stressful Interview, A. M. A. Arch. Neurol. & Psychiat. 79:434, 1958.

3. Grinker, R. R.; Korchin, S. J.; Basowitz, H.; Hamburg, D. A.; Sabshin, M.; Persky, H.; Chevalier, J. A., and Board, F. A.: A Theoretical and Experimental Approach to Problems of Anxiety, A. M. A. Arch. Neurol. & Psychiat. 76:420, 1956.

4. Korchin, S. J.; Basowitz, H.; Grinker, R. R.; Hamburg, D. A.; Persky, H.; Sabshin, M.; Heath, H. A., and Board, F. A.: The Experience of Perceptual Distortion as a Source of Anxiety, A. M. A. Arch. Neurol & Psychiat. 80:98, 1958.

5. Nelson, D. H., and Samuels, L. T.: A Method for the Determination of 17-Hydroxycorticosteroids in Blood: 17-Hydroxycorticosterone in the Peripheral Circulation, J. Clin. Endocrinol. 12:519, 1952.

6. Eik-Nes, K.; Nelson, D. H., and Samuels, L. T.: Determination of 17,21-Hydroxycorticosteroids in Plasma, J. Clin. Endocrinol. 13:1280, 1953.

7. Brown, H.; Willardson, D. G.; Samuels, L. T., and Tyler, F. H.: 17-Hydroxycorticosteroid Metabolism in Liver Disease, J. Clin. Invest. 33:1524, 1954.

8. Reddy, W. J.; Jenkins, D., and Thorn, G. W.: Estimation of 17-Hydroxycorticoids in Urine, Metabolism 1:511, 1952.

9. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. 38:81, 1919.

10. Hamburg, D. A.; Sabshin, M.; Board, F. A.; Grinker, R. R.; Korchin, S. J.; Basowitz, H.; Heath, H., and Persky, H.: Classification and Rating of Emotional Experiences: Special Reference to Reliability of Observation, A. M. A. Arch. Neurol. & Psychiat. 79:415, 1958.

11. Persky, H.: Adrenocortical Function in Anxious Human Subjects: Disappearance of Hydrocortisone from Plasma and Its Metabolic Fate, J. Clin. Endocrinol. 17:760, 1957.

12. Persky, H.: Adrenal Cortical Function in Anxious Human Subjects: Effect of Corticotropin (ACTH) on Plasma Hydrocortisone Level and Urinary Hydroxycorticoid Excretion, A. M. A. Arch. Neurol. & Psychiat. 78:95, 1957.

13. Sabshin, M.; Hamburg, D. A.; Grinker, R. R.; Persky, H.; Basowitz, H.; Korchin, S. J., and Chevalier, J. A.: Significance of Preexperimental Studies in the Psychosomatic Laboratory, A. M. A. Arch. Neurol. & Psychiat. 78:207, 1957.

14. Grinker, R. R.; Sabshin, M.; Hamburg, D. A.; Board, F. A.; Basowitz, H.; Korchin, S. J.; Persky, H., and Chevalier, J. A.: The Use of an Anxiety-Producing Interview and Its Meaning to the Subject, A. M. A. Arch. Neurol. & Psychiat. 77:406, 1957.

15. Glickstein, M.; Chevalier, J. A.; Korchin, S. J.; Basowitz, H.; Sabshin, M.; Hamburg, D. A., and Grinker, R. R.: Temporal Heart-Rate Patterns in Anxious Patients, A. M. A. Arch. Neurol. & Psychiat. 78:101, 1957.

Role of Anxiety in Psychophysiologic Reactions

A Study of Sixty-Seven Postlobotomy Patients Concerning Psychophysiologic Complaints and Symptoms Before and After Operation

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In current literature there seems to be increasing emphasis on the psychogenic aspects of diseases, even those illnesses which are usually considered purely biological in etiology, such as pulmonary tuberculosis.[17] In an effort to clarify the area of "psychosomatic disorders" and to differentiate conversion hysteria, organ neuroses, and typical biological diseases, the psychiatric term "psychophysiologic autonomic and visceral disorder" is now preferred. This term implies that the "symptoms are due to a chronic and exaggerated state of normal physiologic expression of emotion . . . which may lead to structural changes."[2] Psychophysiologic disorders, then, are restricted to those disorders that involve organs and viscera innervated by the autonomic nervous system, rather than by a more voluntary control or perception.

The concept involved in the definition has directed research toward studying each type of disorder and its related personality type or traits. This approach, however, has created conflicting findings and disagreements. For example, Alexander and French[1] and Weiss and English[16] conclude that suppressed crying is the psychogenesis of asthma, while Miller and Baruch[9,11] believe that suppressed hostility and anger or fear of separation from the mother is the important personality factor. The only agreement is that there are prolonged, and often intense, psychological conflicts involved in the etiology of bronchial asthma.

Hamilton[18] observes that, in spite of the many different traits reported for each disorder, there is considerable overlap, virtually invalidating the concept of specific traits (according to his analysis of the reported study by Gildea[3]). Related to Hamilton's conclusion is the astute clinical observation made by Harris[5] that moods and anger affect general health.

Another factor tending to discredit the personality-trait approach is the recent concept of "relative response specificity." Lacey, Bateman, and VanLehn[6] studied the reactions of the autonomic nervous system and came to the conclusion that an individual subject responds with the same type of autonomic response pattern no matter what the stress. This means that an individual responds in the same characteristic manner to different stress situations, whether the stress is anger, fear, hostility, defeat, or the like. This would emphasize the predisposition and learning experiences of the individual patient as possibly being significant etiological factors in the choice of type of reaction, for example, gastric hypermotility.

The possibility of a more basic factor, such as that suggested by May,[8] is indicated. Through work with psychoanalysis, he concluded that there is a basic underlying anxiety in psychosomatic (psychophysiologic) reactions. Although anger, hostility, fear of rejection, etc., are present, a more thorough analysis of the patient frequently

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brings to light the fact that the emotions are "reactions to an underlying anxiety."[19] He also observes that there tends to be an inverse relationship between the person's ability to tolerate conscious anxiety and the appearance of psychophysiologic reactions.

The purpose of this study was to elicit data that might possibly unify and simplify the existing mass of material. The hypothesis was that anxiety is a general factor in or antecedent condition of psychophysiologic autonomic and visceral reactions. Anxiety is an inclusive term for a person's general reaction to stress, often stated to be "tension," "worry," or "vague fears." If anxiety is a condition antecedent to psychophysiologic reactions, then in a situation in which a person has had chronic anxiety and stresses, the incidence of psychophysiologic reactions should be significantly higher in the anxious period than in the nonanxious period. Such a situation occurs in cases of successful prefrontal lobotomy, which usually produces a bland, nonanxious personality.[7,13,15] In the present study the duration of the psychosis was utilized as the anxiety-ridden period.

Subjects

The subjects were 67 patients who had received a prefrontal lobotomy, in which the MacKenzie technique for the surgery was utilized. The subjects were used only because they were lobotomy patients; they were not selected on the basis of having had psychophysiologic disorders. All patients had been rated postoperatively in a previous study[12] as (A) out of the hospital, (B) improved in the hospital, and (C) unimproved in the hospital. Only patients rated A and B were used in this study. Table 1 lists the sex distribution, mean ages for each group, and mean postoperative years, calculated from the date of operation to the date of examination of case material. One woman with a B rating had had two lobotomies; so the second operation was used for the reference point, as that was the one which produced a bland affect.

TABLE 1.—*Mean Ages and Mean Postoperative Years for Each Group of Patients*

Group	No. of Patients	Mean Age	Mean Postoperative Years
Males A	9	49.8	4.9
Males B	9	45.7	5.2
Females A	22	48.1	5.1
Females B	27	43.4	4.1
All A patients	31	48.6	5.0
All B patients	36	43.9	4.4

All the patients prior to the operation had chronic mental illness, and at the time of the operation many were acutely disturbed. Several diagnostic groups were represented in this sample, with a weighting for catatonic and paranoid schizophrenic disorders. The full distribution is recorded in Table 2.

TABLE 2.—*Distribution of Patients According to Diagnosis*

Diagnostic Group	No. of Patients
Schizophrenia, catatonic type	19
Schizophrenia, paranoid type	16
Schizophrenia, other types	9
Manic-depressive psychosis, all types	9
Psychoneurosis, anxiety types	5
Mental deficiency with psychotic reaction	3
Involutional psychosis	3
Miscellaneous	3

Method of Study

All the case-history material available on each of the 67 patients was read, including medical abstracts from other hospitals and doctors, ward charts, letters, and other personal communications, so that all possible references to the patient's mental and physical health would be uncovered. No specific measure or psychological test for anxiety was necessary, as the existence of the psychotic period itself was postulated as evidence of anxiety. The material was abstracted and recorded on file cards, including the patient's name, age, diagnosis, date of operation, postoperative affect, and symptoms, which were grouped according to prepsychotic, psychotic, and postlobotomy periods.

The material from these cards was then tabulated under eight categories, which were composed on the basis of notes from an extensive bibliography. Six categories were formed according to organ systems, based on material as organized by Alexander and French,[1] Hamilton,[4] and Weiss and English[16]; two additional categories were "General Symptoms" and "Unclassified Symptoms." These categories and their inclusions are as follows:

1. *General Symptoms.*—Poor appetite and sleeping; general unexplained malaise; anxiety attacks; nonpathological excessive fatigue and tiredness; unexplained dizziness; "multiple physical complaints with no pathology."

2. Headaches.—"Tension" types; recurring headaches with no pathological explanation; migraine.

3. Allergies and Skin Disorders (including asthma).—Urticaria; psoriasis; recurrent herpes simplex; atopic eczema; neurodermatitis; bronchial asthma.

4. Gastrointestinal Disorders.—Chronic constipation; recurrent diarrhea; functional dyspepsia; chronic "appendicitis"; peptic ulcers; colitis; hemorrhoids.

5. Circulatory Cardiovascular Disorders.—Fainting; recurrent nonpathological epistaxis; tachycardia; essential hypertension; "cardiac neurosis."

6. Genitourinary Disorders.—Functional polyuria; nonpathological impotency; enuresis; dysmenorrhea; premenstrual tension; vaginismus; chronic resistive leukorrhea; nonpathological miscarriage.

7. Respiratory Disorders.—Susceptibility to colds and sore throat; emphysema; chronic bronchitis; chronic cough; unconfirmed tuberculosis; sinusitis; vasomotor rhinitis.

8. Unclassified Symptoms.—Symptoms that either did not fit into other categories or had questionable pathological etiology, such as lumbago, exophthalmic goiter, obesity, addiction to alcohol, rheumatoid arthritis, stuttering and other speech impediments, and "somatic delusions."

It must be remembered that symptoms were evaluated in the light of the whole case history and that every effort was made to substantiate the existence of an actual pathological condition (nonpsychogenic in etiology). The life events of the patient corresponding to the time of the illness, as well as all concurrent medical reports for pathology in relation to the illness, were checked. To illustrate, if a patient complained of excessive fatigue, the records were checked for low hemoglobin, infections, and drugs that could make the patient sleepy, and for nonmedical events, such as overwork, insomnia, signs of depression, discouragement, or pressing personal problems. Each symptom was evaluated in the above manner and the appropriate category checked. For each patient a category was checked if one or more symptoms appeared under it; it was *not* checked each time the same symptom appeared, as it was wished to avoid confusion with recurrence of old symptoms; that is, when an old symptom recurred, it was not counted twice. Multiple symptoms of a category appear in the data as only one check for that category.

Instead of a dubious matching of subjects differing in age, diagnosis, and length of time in the hospital, each patient was used as his own control. The patient was compared with himself for the appearance of symptoms during the prepsychotic, psychotic, and postlobotomy periods. The date of the psychotic period was set at the time of first admission to a mental hospital, as information from relatives was often too vague to determine onset. In this way, the same criterion was applied to each patient.

Results

Inspection of Table 3 reveals a fairly constant population of symptoms during the prepsychotic and psychotic periods, but a great change, a notable loss of symptoms, from the psychotic to the postlobotomy period. That this occurred in all categories of psychophysiologic symptoms is shown in Table 4. The constancy of symptoms during the prelobotomy period was a population constancy only because 55 patients changed the old symptoms of their prepsychotic period for new symptoms during the psychotic period. This lability of psychophysiologic symptoms is well known. This exchanging of symptoms during the prelobotomy period contrasts with the apparent freedom from psychophysiologic symptoms of 47 patients in the postlobotomy period. For those who still manifested symptoms during the postlobotomy period

TABLE 3.—*Distribution of Psychophysiologic Symptoms by Periods for Sixty-Seven Lobotomized Patients*

	Prepsychotic	Psychotic	Postlobotomy
Total symptoms tallied	104	115	28
No. of patients having one or more categories of symptoms	59	66	20
No. of patients with no symptoms	8	1	47
Average symptoms per affected patient	1.76	1.74	1.40

TABLE 4.—*Number of Symptoms Checked in Each Category for Each Period*

Category	Prepsychotic	Psychotic	Postlobotomy
1	9	11	7
2	8	10	3
3	8	11	4
4	12	20	5
5	5	11	4
6	21	8	0
7	10	10	0
8	31	31	5
Totals	104	115	28

TABLE 5.—*Significance of Changes (t-Test) Between Periods*

Periods Compared	No. of Patients	t-Test Value	Significance
Prepsychotic vs. postlobotomy	67	6.74	Beyond 0.01 level
Prepsychotic vs. psychotic	67	0.98	Not significant
Psychotic vs. postlobotomy	67	11.15	Beyond 0.001 level

the range of decrease of symptoms was from 1.74 to 1.40 per affected patient.

Since each patient was his own control, the comparison between periods can be brought down to the changes in the individual patient. Table 5 corroborates what has been found in Tables 3 and 4, namely, that a statistically significant difference exists between psychophysiologic symptoms during preceding periods and the postlobotomy period, but that before lobotomy the level of symptoms stayed fairly constant.

Reliability of Data Collection and Categorization of Case Material

Initially one of the investigators (J. F.) did all the reading and checking of case material. A blind reliability check was done by another investigator (T. M. C.), using the same research procedure, to see whether the results would be verified. The latter investigator was kept ignorant of the previous ratings so that he would be uninfluenced by a desire to make his figures correspond to the original data.

The agreement between the two raters was examined in two ways: First, whether they could discriminate concordantly the presence or absence of psychophysiologic symptoms or complaints in each of the 67 patients, and, second, whether the number of categories of symptoms they obtained for each patient was the same.

Table 6 gives an answer to the first question. While only a chance agreement shows up during the prepsychotic period, the concordance is statistically significant ($P<0.01$) during the psychotic and postlobotomy periods. Apparently, when the records are more adequate, the case readers

TABLE 6.—*Concordance of Two Raters on Whether Each of Sixty-Seven Patients Was Free or Not of Psychophysiological Symptoms*

	Prepsychotic	Psychotic	Postlobotomy
Agreement	37	63	48
Disagreement	30	4	19
Concordance	55%	94%	72%

can readily discriminate between the presence and the absence of a psychophysiologic disorder in a patient. That this fundamental question can be reliably answered makes credible the loss of symptoms after lobotomy shown in Tables 3, 4, and 5.

The second question, as to whether the agreement of the raters extends to the categorization of symptoms, was less successfully answered. The rank-order correlations between the raters for number of symptoms per patient were in the 30's (significantly different from zero, but still with only fair predictability from one rater to the other). Even when individual differences are averaged out by finding rank-order correlations for the total frequencies of symptoms in the eight categories, the ρ values are not higher than 0.75 and 0.72 for the prepsychotic and postlobotomy periods, respectively, and only 0.39 for the psychotic period. A clue to the reason for these unsatisfactory correlations on the second question comes from the fact that the second rater (T. M. C.) did not have a large background in biological studies and tended to check more categories than the first rater (J. F.), who could more readily see the inclusive syndrome. For example, what J. F. classified under a single category of migraine headache syndrome (headache with nausea, vomiting, and visual disturbances), T. M. C. put under three categories. One could anticipate higher reliability correlations than those secured in this study if the case readers and categorizors were clinically expert. However, the conclusion of this study that a significant drop in psychophysiologic symptoms occurred after lobotomy can be reached from analysis of the data of either

of the two raters, although Tables 3, 4, and 5 are based upon the records of J. F.

Comment

These results support the hypothesis that when anxiety is alleviated, there is a concurrent reduction in psychophysiologic symptoms and complaints. There is a statistically significant decrease in frequencies of reported symptoms following the bland affect produced by the lobotomy operation. The data indicate that the reduction of severe anxiety is of benefit to general health in that frequencies and intensity of disorders in all, rather than specific, categories were reduced. This would seem to indicate, then, that in some persons anxiety is a basic factor in psychophysiologic symptoms and complaints. At this time we should not generalize far beyond the experimental population, until the indicated trend has been verified in other samples.

Several factors should be kept in mind while interpreting these results. First, because of the nature of the data, some spurious losses of symptoms were found. Some symptoms, e. g., drug addiction and alcoholism, would be precluded by the hospital situation. Also, there were physical changes which could effect false relationships, e. g., the menopause, which would preclude psychogenic dysmenorrhea and miscarriage. The actual number of cases affected by these two factors was small in proportion to the total number of patients, 8 out of 67. Counteracting any effects of these factors was the commoner occurrence of counting a symptom as appearing, even though the patient or his relatives reported it reduced in frequency or intensity.

Second, it is unknown exactly how much the lethargy of the patient may have affected his reporting of symptoms. In both unilateral and bilateral lobotomized patients experimentally addicted to morphine before the operation, Spingarn[14] has reported lethargy and absence of complaints of symptoms of morphine withdrawal. It is also generally known that the postlobotomy patients often continue to have the same mental symptoms, but they are no longer bothered by them. Something similar may occur in the realm of physical symptoms—they may still be present, but the patient does not bother to report them. However, relatives and others in daily contact with the patients attested to the disappearance of such obvious symptoms as those of asthma.

Third, because the postlobotomy period was shorter in years than the prepsychotic and psychotic periods, there has been less time for accumulation of symptoms in the postlobotomy period. The differences between periods recorded in Table 4, however, are so large that it does not seem likely that a longer time in the postlobotomy period would produce enough symptoms to decrease appreciably the level of confidence to nonsignificance.

Fourth, clerical problems constantly intruded because of the nature of the case materials. Records were kept by many doctors, under different systems, and, although the amount of paper was prodigious, the data wanted were sometimes missing, incomplete, or not recorded. In spite of these difficulties involved in using the case materials, this study showed that reliable data could be obtained by two independent investigators.

In view of these interesting findings, we feel that further studies, with similar patients, should be undertaken, in which case material could be analyzed to see whether there is a comparable reduction in psychophysiologic symptoms and complaints after lobotomy operations. Moreover, the results of other types of psychiatric treatments which alleviate anxiety, e. g., the tranquilizing medications, might be studied and analyzed in a similar manner.

Summary

An experimental study has been made of the hypothesis that anxiety plays a decisive role in the occurrence and maintenance of psychophysiologic symptoms and complaints.

For this study, the records of 67 postlobotomy patients were analyzed in order to discriminate and tally psychophysiologic symptoms and complaints for the prepsychotic, psychotic, and postlobotomy periods. The data from the records were then categorized according to a check list composed from the literature on psychophysiologic disorders. Since the results showed a significant difference between the frequencies of symptoms for the prepsychotic and psychotic periods and those for the postlobotomy period, a blind reliability study was done to check the collection of data and categorization of material.

The two case readers and raters agreed beyond chance ($P<0.01$) on the presence or absence of a psychophysiologic disorder in a patient where the records were more adequate, i. e., in the psychotic and postlobotomy periods. They did not agree on the characterization of the disorder in terms of the number of categories, probably because of differences in background in biological sciences, and because of the difficulty of teasing out of voluminous records the essence of a syndrome, in order to quantify it. This should raise reservations about the categorization of the symptoms and would be absolutely critical for a study of shift of symptoms, i. e., from prepsychotic to psychotic periods. But the agreement of the raters on the presence or absence of a psychophysiologic condition gives confidence that a significant drop in symptoms occurred after lobotomy.

The support from this study of the hypothesis that a relationship exists between anxiety and psychophysiologic symptoms and complaints has interesting theoretical implications and suggests the desirability of further study of other groups of patients whose anxiety is alleviated by the use of other psychiatric treatments, such as the tranquilizing medications.

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REFERENCES

1. Alexander, F., and French, T. M., Editors: Studies in Psychosomatic Medicine: An Approach to the Causes and Treatment of Vegetative Disturbances, New York, The Ronald Press Company, 1948.

2. American Psychiatric Association: Diagnostic and Statistical Manual: Mental Disorders, prepared by the Committee on Nomenclature and Statistics of the American Psychiatric Association, Washington, D. C., 1955, pp. 29-31.

3. Gildea, E. F.: Special Features of Personality Which Are Common to Certain Psychosomatic Disorders, Psychosom. Med. 11:273, 1949.

4. Hamilton, M.: Psychosomatics, with Foreword by D. R. MacCalman, New York, John Wiley & Sons, Inc., 1955.

5. Harris, I. D.: Mood, Anger and Somatic Dysfunction, J. Nerv. & Ment. Dis. 113:152, 1951.

6. Lacey, J. I.; Bateman, D. E., and VanLehn, R.: Autonomic Response and Specificity: An Experimental Study, Psychosom. Med. 15:8, 1953.

7. Landis, C.; Zubin, J., and Mettler, F. A.: The Functions of the Human Frontal Lobe, J. Psychol. 30:123, 1950.

8. May, R.: The Meaning of Anxiety, New York, The Ronald Press Company, 1950.

9. Miller, H., and Baruch, D. W.: A Study of Hostility in Allergic Children, Am. J. Orthopsychiat. 20:506, 1950.

10. Miller, H., and Baruch, D. W.: Psychological Dynamics in Allergic Patients as Shown in Group and Individual Psychotherapy, J. Consult. Psychol. 12:111, 1948.

11. Miller, H., and Baruch, D.: Psychosomatic Studies of Children with Allergic Manifestations—Maternal Rejection: A Study of 63 Cases, Psychosom. Med. 10:275, 1948.

12. Niswander, G. D.; Cummings, W. E.; Oakey, K. B., and Holt, E. K.: Results of Lobotomy Operations, Dis. Nerv. System 18:294, 1957.

13. Reiner, E. R., and Sands, S. L.: Lobotomy and Psychopathology, A. M. A. Arch. Neurol. & Psychiat. 65:48, 1951.

14. Spingarn, J. A.: Brain Injury and Morphine Withdrawal, Psychol. Bull. 54:65, 1957.

15. Weider, A., Editor: Contributions Toward Medical Psychology: Theory and Psychodiagnostic Methods, New York, The Ronald Press Company, 1953, Vol. I.

16. Weiss, E., and English, O. S.: Psychosomatic Medicine: Clinical Application of Psychopathology to General Medical Problems, Philadelphia, W. B. Saunders Company, 1947, pp. 419-437.

17. Hamilton,[4] p. 50.

18. Hamilton,[4] pp. 207-208.

19. May,[8] p. 52.

Periodic Phenomena and the Thyroid

I. Abnormal But Regular Cycles in Behavior and Metabolism Produced in Rats by Partial Radiothyroidectomy

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Under normal conditions men and women do not show any readily detectable periodicity in behavior, mood, or metabolism, except, of course, for the 24-hour cycle of sleep and waking and the 28-day menstrual cycle of females; however, under certain kinds of illness, in some instances mental, in others physical, men and women show regularly recurring phenomena that may affect both mind and body.

Records are at hand of many mentally ill persons who have the most regular attacks during which they may undergo marked pathological changes in personality, thinking, and attitude toward life in general, while in the intervals between the attacks they are entirely normal. During the attacks any one person may show one or more of the following symptoms: sadness, elation, stupor, uncontrollable suspiciousness, fear, lethargy, and aggressiveness; this person may also show one or more of the following physical symptoms: fever, elevated pulse rate, increased blood pressure, headache, and pain in joints, muscles, or internal organs. The mental symptoms, however, predominate.

In some persons the attacks may come once a day; in others every other day, and in still others at intervals of 10-30 days, or even months or years. In some persons the attacks are longer than the free intervals, in others shorter. They may persist for a few months or for years or for a lifetime. Onset is apt to be quite sudden, as is also the cessation.

Records are at hand of an equally large number of persons who have regular attacks of physical illness during which they suffer from violent and incapacitating disturbances, but between which they enjoy normal health. During the attacks any one person may have one or more of the following signs or symptoms: neutropenia, high fever, pain in the joints or internal organs, swelling of the legs, arms, or joints, loss of appetite, insomnia, and urticaria; however, although the physical symptoms predominate, one or more of the following mental or emotional symptoms may be manifested: sadness, aggressiveness, and stubbornness. The attacks may come at intervals of 12, 24, or 48 hours, 6 to 7 days, 20 or 40 days, or several months; 13-14 and 20-22 days, however, are the commonest intervals. One patient experienced swelling of the knees every 21 days during a lifetime of over 70 years. As in periodic mental illness, the transition between the normal and the abnormal condition may be very sharp, lasting sometimes only a few minutes. The attacks may persist for months or years or, as previously noted, a lifetime.

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Carried out under grants from the U. S. Public Health Service and the National Science Foundation. Brief accounts of some of the results of the present study were included in a more general summary of our studies on cycles presented before the American Psychopathological Society, 1953,[22] the Laurentian Hormone Conference, 1955.[23]

The origin of these various types of periodic phenomena has long remained a mystery. Psychiatrists and internists alike have experienced difficulty in imagining any mechanism within the body that could function with such regularity and at such a wide range of frequencies. Some investigators have sought in vain for their origin in recurring phenomena outside the body.

Chance observations made many years ago on the glandular control of spontaneous gross bodily activity of rats may help to throw some light on the origin and nature of these periodic phenomena of man. In these experiments it was found that abnormal but regularly recurring cycles of spontaneous activity (as measured in revolving drums) and food intake can be produced by (1) partial thyroidectomy (Richter,[20] 1933) or (2) section of the pituitary stalk (Richter,[21] 1933). The cycles produced by each method have fairly specific frequencies and characteristics.

In recent years we have repeated these observations and have made a more intensive study in each instance of the various factors involved in the production of the cycles. The present paper deals only with periodic phenomena that result from one type of interference with the function of the thyroid gland.

In our earlier study on the effects of thyroidectomy on spontaneous activity, it was found that attempted complete thyroidectomy gave results varying from no change in activity to the production of total inactivity. Of special interest for the present purpose is the finding that in a few of the rats the fluctuations in activity seemed to come in cycles, each one consisting of an active and an inactive phase. At the start the active phases were 20-45 days in length, but later became shorter. The length of the inactive phases remained quite constant, 10-18 days. The rats ate less during the active phases and more during the inactive phases. Such cycles were found in 3 of 14 rats.

Autopsy findings showed that the thyroid had not been completely removed in any of the animals, with the possible exception of one, an animal that became almost totally inactive. Minute, scarcely detectable nodules of thyroid tissue were found at different places on the trachea in all of the other rats, and, from what has been learned since, it is likely that thyroid tissue remained in other parts of the neck as far removed as the thymus gland (Asling et al.,[1] 1957). Thus, to produce fluctuations, particularly regular ones, it seemed to be essential to remove all except a minute amount of thyroid tissue, but not all.

Over the course of years further attempts were made from time to time to determine whether these regular cyclic fluctuations could be produced by other surgical methods of removing the thyroid, but no further progress was made; in fact, in most instances the amounts of tissue that remained after careful dissection under a dissecting microscope sufficed to maintain normal activity. For this reason, attempts to produce abnormal but regular cycles by surgery were abandoned.

In 1950 a renewed attempt to produce abnormal but regular cycles in activity and metabolism was made by destroying the gland with radioactive iodine, I^{131}. I^{131} reaches thyroid tissue no matter where located and when given in graded doses destroys definite amounts of the thyroid tissue. Thus, this method has several advantages over surgical removal.

The following experiments are concerned with the question: Can abnormal but regular cycles in behavior and metabolism be produced in rats by partially destroying the thyroid with I^{131}? If so, (1) are the cycles the same as those that resulted from surgical partial thyroidectomy; (2) can they be produced in a higher proportion of animals; (3) does I^{131} have any generalized effects that influence the appearance of cycles; do the abnormal cycles appear at once after treatment, or must the rat be exposed to the thyroxine deficiency for

some time before they make their appearance; (4) do the results throw any light on the underlying mechanisms responsible for the production of the cycles, and, finally (5), do these cycles produced in rats bear any resemblance to the cycles seen under pathological conditions in man?

Methods

In these experiments the rats were housed in individual activity cages, consisting of a small living compartment 3½×5×11 in. (containing a nonspillable food cup and graduated water bottle), a revolving drum 13 in. in diameter and 6 in. wide, and a cyclometer for recording revolutions of the drum (Richter and Wang,[87] 1926). Records were made daily of running activity, vaginal smears, and food and water intake, and weekly of body weight. The construction of the cages prevented coprophagy (Richter and Rice,[86] 1942).

The conditions in the laboratory were kept as constant as possible from day to day and free from all periodic procedures except for the daily routine. Temperature was maintained near 75 F (without air conditioning) except during short heat spells during the summer; lights were turned on at 9 a. m. and off shortly after 5 p. m. Records were taken at as nearly as possible the same time (9-10 a. m.) each day, and the food cups and water bottles were filled at the same hour. The drums were tested at frequent intervals to make certain that they revolved equally freely at all times.

The stock diet was prepared several times a week and was mixed with the same ingredients, in the same way throughout (graham flour 72.5%, casein 10%, skim milk powder 10%, butter 5%, calcium carbonate 1.5%, salt 1%).

The 16 female rats used for this study came from our colony. They were tame and not readily disturbed by noises or handling. Only females were used, since in the thyroidectomy experiments the rats showing abnormal but regular cycles in activity were females, and since in females the vaginal smears give a good indication of the condition of the reproductive tract. Observations on males are now in progress and will be reported later.

The number of rats used in these experiments necessarily had to be small, since each rat was subjected to an intensive study over many months or years, involving literally many thousand daily readings. For this reason the results will, to a large extent, have to be presented as records of individual rats, rather than as statistical averages of many rats.

The rats were placed in the activity cages at an average age of 41 days. During the first few days they were not very active; after that they became progressively more active. Several weeks later, while their activity was still increasing, treatment with I^{131} was initiated. The isotope (with no carrier added) was given by stomach tube at a dose of 100μc. (1 ml.) to 14 rats and in a dose of 200μc. to 2 animals.

The 100μc. dose was used, since we wished to destroy only part of the gland and not to damage the parathyroids or any of the surrounding tissues. This is less than one-third the dose (325μc.) that will temporarily destroy a large part of the *gland*; it is less than one-eighth the dose needed for permanent destruction of the gland (825μc.); it is only two and a half times as large as a dose (38μc.) that fails to produce any detectable changes in the gland at all (Goldberg et al.,[9] 1950).

If, after a reasonable time, this dose did not produce any detectable cyclic changes, it was repeated until cycles appeared or the activity became low and flat. In only one instance did one dose suffice to bring out abnormal cycles; in the others two, three, or four doses were needed. A reasonable time, 40 days or longer, was allowed between the administration of successive doses. In some instances intervals as long as 130 days elapsed.

At the end of the experiment the rats were killed and autopsied, and the organs were weighed and fixed for histological studies.

Results

Normal Control Rats

Daily observations of spontaneous running activity, food and water intake, and body weight have been made on several hundred normal, untreated rats. Figure 1 shows part of a typical daily record of a normal female rat. The ordinates show running activity in number of revolutions of the drum, food intake and body weight in grams, and cornified cells in per cent of the total number of cells in the vaginal smears. This rat was placed in the activity cage at an age of 42 days. Like most young rats, when placed in the activity cage, it was quite inactive for the first few days, but then quickly became more active. The four- to five-day peaks of activity associated with estrus appeared at this time. They recurred with great regularity and coincided with the appearance of cornified cells in the vaginal smears. After 20 days activity

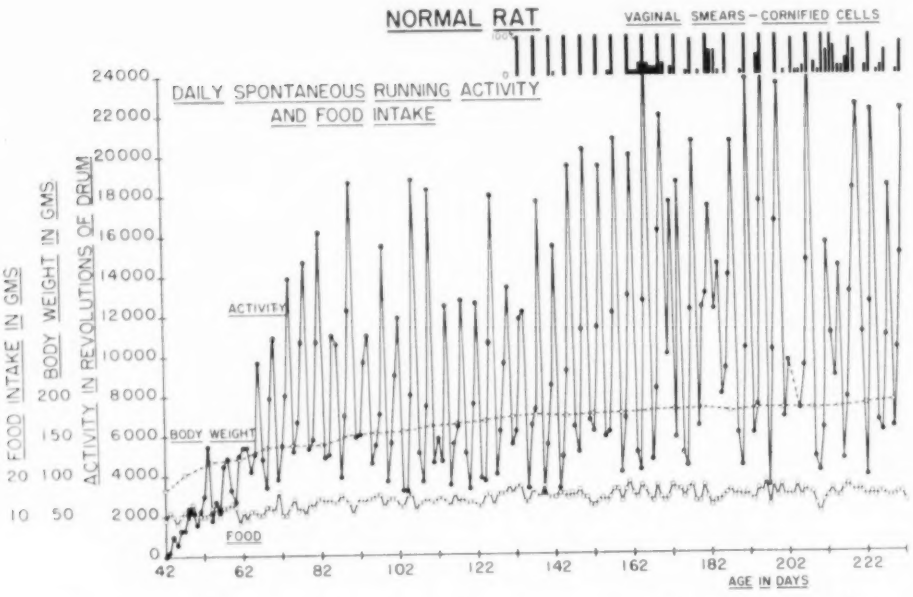

Fig. 1.—Graph for a normal female rat showing daily records of spontaneous running activity, food intake, and vaginal smears, and weekly records of body weight.

reached an average level of 8000 revolutions and from then on increased at a much slower rate. Food intake tended to remain fairly constant and did not show the four- to five-day changes. Activity and food intake continued at much the same levels for many months.

Under the experimental conditions of our laboratory, the four- or five-day estrous cycle appears in daily running activity and in the vaginal smears in all of the normal rats of our colony. It appears in food intake and body weight in only a small number of animals and rarely, if at all, in water intake. Rats kept in a soundproof chamber at a closely controlled environmental temperature may show this cycle in food intake, in body weight, and even in body temperature in a larger proportion of animals (Brobeck, Wheatland, and Strominger,[4] 1947).

Of interest in relation to the results of the present study is the existence of an inverse relationship between spontaneous activity, on the one hand, and food intake, body weight, and body temperature, on the other; that is, on the day of the cycle that the rat runs the most, it eats the least, and the reverse, and in all instances body weight and body temperature parallel food intake.

It is of note that ovariectomy reduces activity to a flat low level, abolishes the four- or five-day cycles, and increases food intake and body weight, and that pregnancy and pseudopregnancy likewise reduce activity and increase food intake and body weight, whereas, by contrast, treatment with estrogens increases running activity and decreases food intake (Wang,[40] 1923).

Rats Treated with I^{131}

Effect on Spontaneous Running Activity. Level of Activity: In most instances the first treatment with a 100μc. dose of I^{131} reduced running activity to a lower level, not at once, but within the following 10-15 days. In some instances the second treatment reduced the activity to a flat low level, but in others a final sharp drop did not occur until after the third or fourth treatment. The three curves in Figure 2 illus-

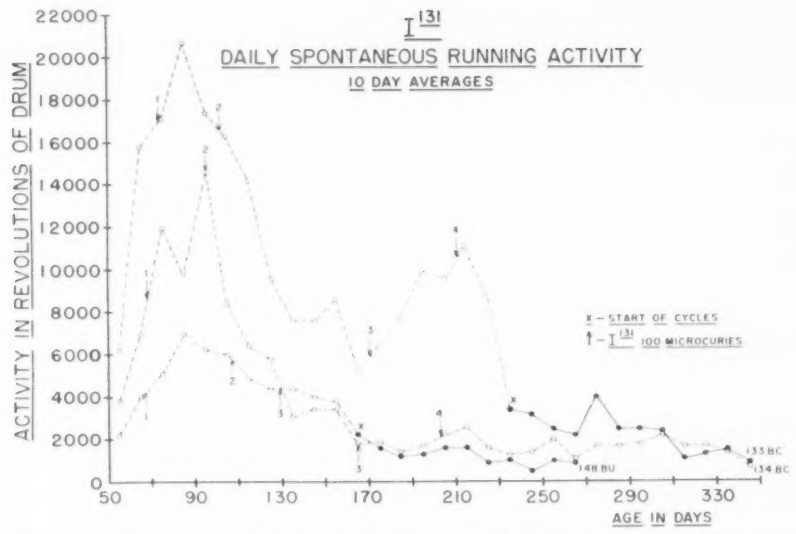

Fig. 2.—Graph for three female rats illustrating three different effects of I^{131} treatment on daily spontaneous running activity (10-day averages): Type I (133BC); Type II (148BU); Type III (134BC). The arrows show the times of the successive treatments with I^{131} (100μc.); *X* marks the appearance of the inactive phase of the first abnormal cycle.

trate three different effects. The ordinates give average daily running activity for 10-day periods, and the abscissas, age in days. The arrows indicate treatment; the crosses, time of first appearance of abnormal cycles, and the solid lines with circles, presence of abnormal cycles. The most active of the three rats (133BC) received four treatments of I^{131} over a 140-day period. During the first 30 days in the cage its activity increased from an average of 6100 revolutions per day to 17,100 revolutions per day. After the first treatment, at an age of 82 days, its activity still increased for another 10-day period, before it reached a peak and began to decrease. A second treatment 28 days later had no detectable effect. A low point was reached at 166 days. Activity increased again in spite of a third treatment, at 178 days. A fourth treatment, at 220 days, resulted in a final sharp drop from 10,400 to less than 4000 revolutions per day, and the appearance of abnormal cycles (indicated by *X*), which will be described below. The next most active of these three rats (134BC) also received four treatments. After the first treatment its activity continued to increase and reached a peak of 14,500 revolutions after 30 days, coincident with the second treatment. Its activity then fell off at a rapid and steady rate for the next 60 days, to an average of 2000 revolutions, at which it remained in spite of the third and fourth treatments. This rat did not show any abnormal cycles. The least active of the three rats (148BU) had three treatments. Here, again, activity continued to increase for 20 days or more after the first treatment, before it started to decrease. The second treatment had no detectable effect, but the third was followed after 20 days by a sharp drop and the appearance of abnormal cycles (*X*), which likewise will be described in more detail below.

Except for one possible instance, none of the rats showed the abnormal cycles until after they had become much less active than before treatment.

Abnormal Activity Cycles: The abnormal cycles that appeared were more regular than any of those seen in the partially thyroidec-

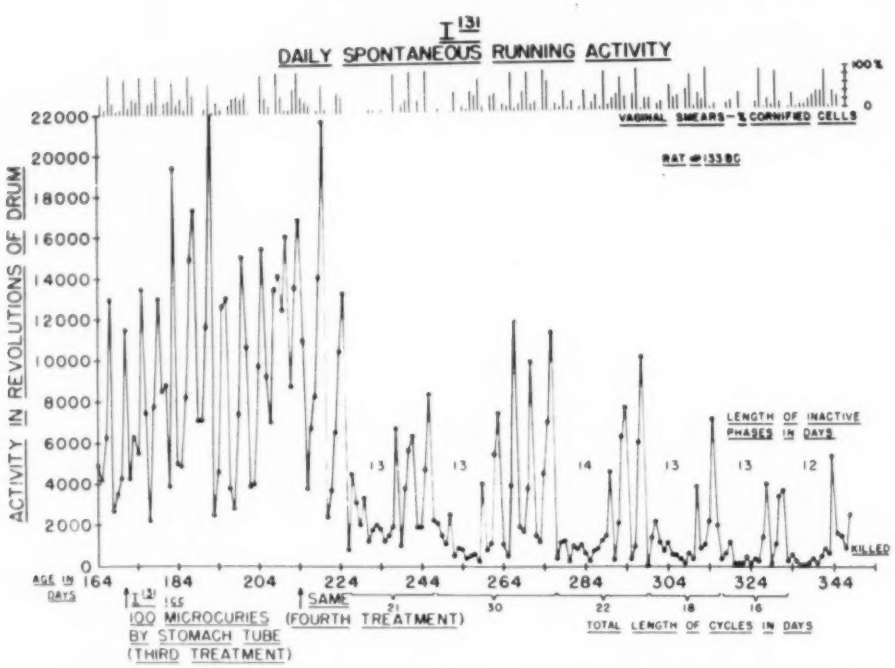

Fig. 3.—Graphs showing abnormal cycles in daily spontaneous running activity and vaginal smears that appeared in a Type I rat (133BC) after four treatments with I^{131} (100 μc.).

tomized rats, and, furthermore, they appeared in a higher proportion of the rats.

Figure 3 gives daily activity and vaginal smear records of a rat (133BC) whose 10-day average record was shown in Figure 2. The ordinates give activity in number of revolutions of the drum, and the abscissas, age in days. The cycles did not appear until after a fourth treatment with I^{131} (age 214 days). The record starts at 164 days, that is, a short time before the third treatment, when the activity had already dropped to a lower level. The four- or five-day estrous cycles were present and regular before and after the third treatment. On the 11th day after the fourth treatment, activity dropped to a much lower level, at which it remained for 12 days, and at this time there was no evidence of four- or five-day estrous peaks; the first estrous peak came on the 13th day after the sudden drop. There then followed two estrous cycles and another long inactive period, lasting 13 days; then followed a long activity period with five estrous peaks, and an inactive period with no estrous cycles. The following periods of activity became progressively shorter, whereas the inactive periods (peak to peak) remained the same in length (12 to 14 days). The total length of the first abnormal cycle was 21 days; the lengths of the following cycles were 30, 22, 18, and 16, respectively. The vaginal smears showed 100% cornification on days of peak activity during each active phase of the cycle and few or no cornified cells during the inactive intervals.

Figure 4 shows the daily-activity and vaginal-smear record of another rat, beginning at 58 days and ending at 429 days. This rat had two treatments of I^{131} at ages 68 and 97 days, respectively. The first treatment had little effect on the four- or five-day estrous peaks, whereas the second treatment was followed, after 11 days, by a sharp drop to a low level and the complete disappearance of the four- or five-day peaks. The first inactive period, of 13 days, was

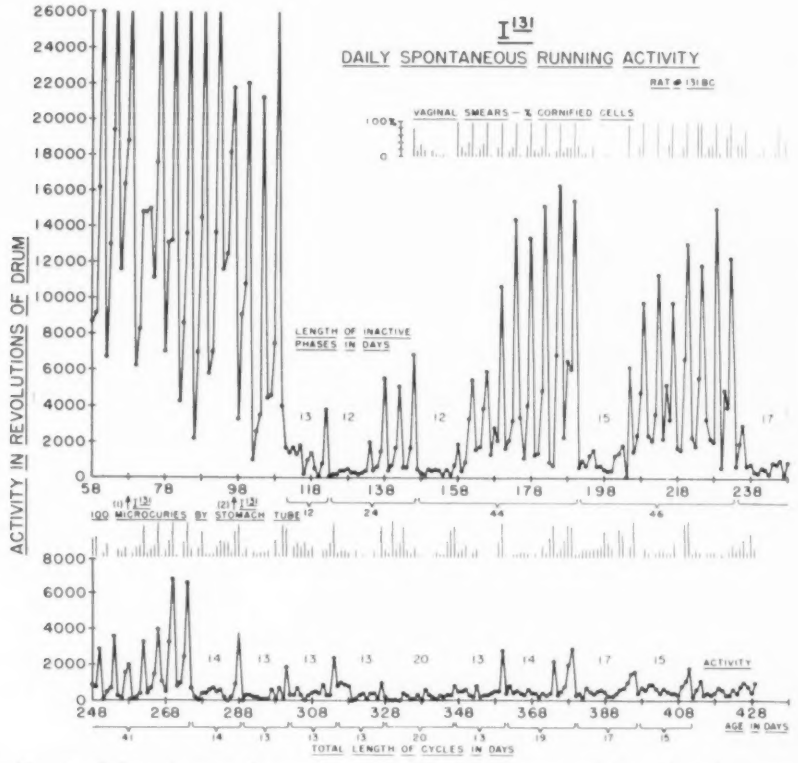

Fig. 4.—Graphs showing abnormal cycles in daily spontaneous activity and vaginal smears that appeared in another Type I rat (131BC) after four treatments with I^{131} (100μc.).

followed by a burst of activity, lasting 1 day, and another inactive period, of 12 days; then followed a period of activity with four 4-day estrous peaks and another inactive period of 12 days, and three long periods of much greater activity, with 8, 7, and 6 full estrous cycles, respectively, and inactive periods of 15 and 17 days, respectively. Up to this point the total lengths of the cycles were 12, 24, 44, 46, and 41 days, respectively, all the variations being accounted for by changes in the length of the active periods. Then the lengths of the active periods showed a sudden decrease to one to two days, whereas the lengths of the inactive periods remained essentially unchanged. Thus, the total lengths of the following cycles were 14, 13, 13, 13, 20, 13, 19, 17, and 15 days. Here, again, the vaginal smears showed 100% cornification on the peak days of activity and few or no cornified cells during the inactive periods.

Figure 5 illustrates another type of effect of the treatment. It gives the record of Rat 148BU, whose 10-day average daily activity curve is shown in Figure 2. This rat had three treatments. Twenty-six days after the third treatment it showed its first cycle. Its activity dropped to a low level for 14 days. From then on, unlike the rats in Figures 3 and 4, it showed only single-day bursts of activity, separated by inactive periods. The vaginal smears showed 100% cornification on days of peak activity and for several days preceding.

Figure 6 shows the record of Rat 134BC, whose average daily activity was presented in Figure 2. This rat had four treatments. Eighteen days after the second treatment activity dropped to a quite low and fairly

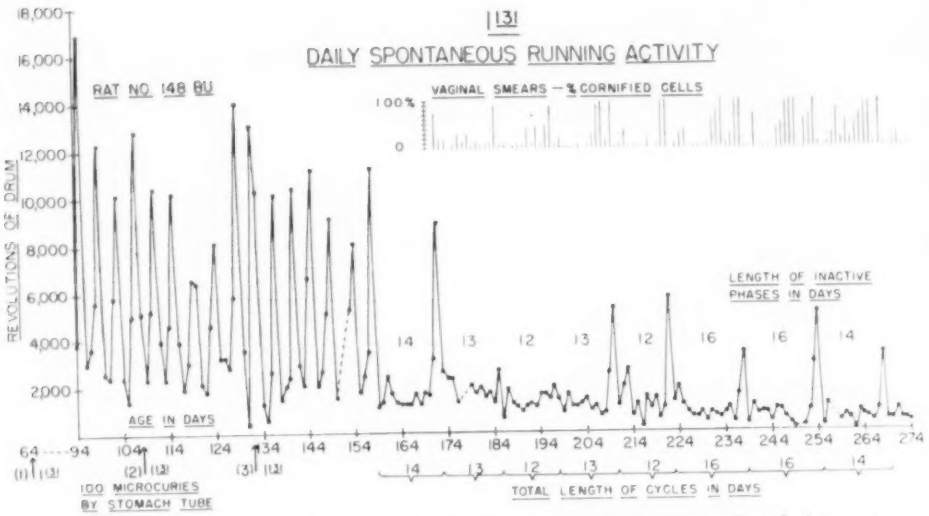

Fig. 5.—Graph showing abnormal cycles in daily spontaneous activity and vaginal smears that appeared in Type II rat (148BU) after three treatments with I^{131} (100μc.).

constant level. The third and fourth treatments had no further detectable effect. There were no abnormal cycles. The vaginal smear record showed 100% cornification every four or five days, indicating the lack of any interference with the estrous cycle.

Incidence of Activity Cycles: If we use the presence of the inactive phase of 12-16 days in length as the essential characteristic, then 8 of 16 rats, or 50%, showed the abnormal cycles. Six of the eight rats had cycles of the kind seen in Figures 3 and 4 (Type I); the remaining two had cycles of

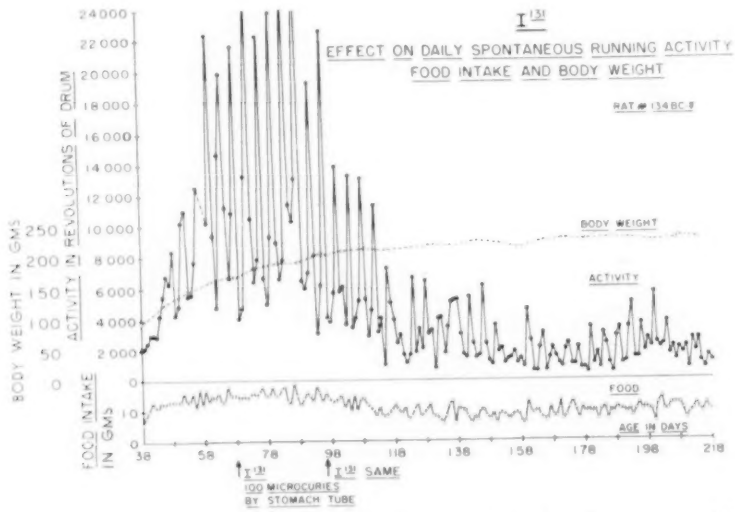

Fig. 6.—Graph showing absence of abnormal cycles in daily spontaneous activity and vaginal smears in Type III rat (134BC) after four treatments with I^{131} (100μc.).

TABLE 1.— *Types of Effect of I^{131} in Rats*

Type of Effect	Rat	Age, in Days, at First Treatment	Number of Treatments	Latency Period, in Days, After First Treatment Before Appearance of: Decrease in Activity	First Inactive Phase	Decrease in Food Intake	Decrease in Water Intake	Decrease in Rate of Growth
				100μc.				
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
I	133BC	74	4	42	151	26	--	--
	131BC	69	2	42	42	23	48	--
	154BU	66	2	43	43	15	55	--
	153BU	66	3	50	81	28	61	95
	146BU	66	1	27	27	26	59	39
	145BU	66	3	47	70	47	49	97
	Average	66.1	2.5	41.8	69.0	27.5	54.4	77.0
II	152BU	68	2	41	46	20	46	18
	148BU	67	3	32	88	28	33	--
	Average	67.5	2.5	36.5	67.0	24.0	39.5	18.0
III	134BC	69	3	30	--	19	13	--
	146BF	107	2	5	--	11	11	--
	149BU	66	33	47	--	32	19	45
	147BU	66	3	25	--	24	24	50
	153BF	107	2	15	--	14	22	--
	132BC	74	4	42	--	24	21	--
	Average	81.5	2.8	27.3		20.6	18.3	47.5
				200μc.				
	304BX	89	1	13	--	15	11	--
	315BX	87	1	10	--	22	21	19
	Average	88.0	1.0	11.5		18.5	16.0	19.0

the kind shown in Figure 5 (Type II); the other eight rats showed flat curves or irregular fluctuations, with no indication of the presence of the inactive periods (Type III). Table 1 lists the rats showing each type of effect (Columns 1 and 2), as well as their ages and number of treatments (Columns 3 and 4).

That the abnormal long-activity cycles may have been present, but somehow prevented from making their appearance, in some of the eight Type III rats is shown by the record in Figure 7. This rat was fairly inactive before the I^{131} treatment (200μc.) at an age of 89 days. Afterward it became even less active, and there were

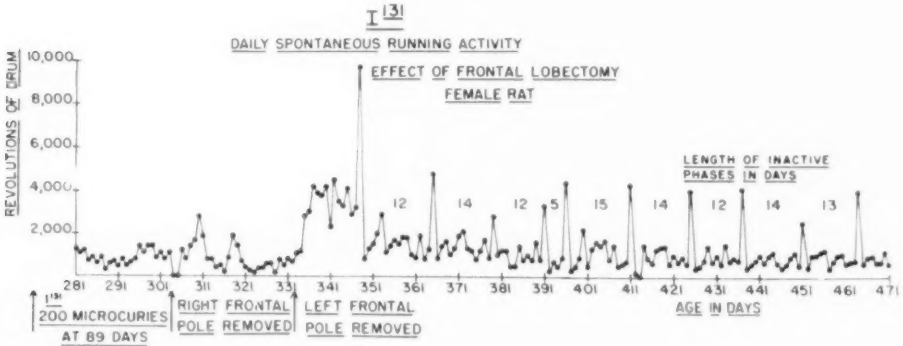

Fig. 7.—Graph of rat that failed to show cycles in daily spontaneous activity after one treatment with I^{131} (200μc.) but which showed them after removal of both frontal poles of the brain.

no abnormal cycles of any type. Then, at the age of 304 and 331 days, respectively, the right and left frontal poles of the brain were removed. From the results of earlier experiments we know that these operations make a normal rat more active, apparently through the removal of inhibitory influences of the frontal lobes, but they do not bring out any abnormal cyclic changes in activity (Richter and Hawkes,[25] 1939). After the first operation in this animal, activity showed only two small bursts; after the second operation, however, activity increased and after 20 days showed the same regular abnormal cycles as were seen in the record in Figure 5 (Type II) with single-day bursts separated by inactive periods of 12-15 days in length.

Latency Period of Decrease in Activity and Appearance of Abnormal Cycles: The first treatment with I^{131} decreased the spontaneous activity of all 16 rats, but only after a latency period of several weeks, as may be seen in Table 1 (Column 5). This

TABLE 2.—*Total Length of Successive Cycles, in Days*

	Type I						Type II		Type III Frontal Lobectomy
	133BC	131BC	154BU	153BU	146BU	145BU	152BU	148BU	304BX
		12							
		24							
	21	44		44	77				
	30	46	28	21	18				
	22	41	31	20	34	29			
	18	14	16	15	18	12	15	14	17
	16	13	23		16	13	20	13	14
	Killed	13	15		16		18	12	17
		13	9				16	13	15
		20	19				26	12	14
		13	15				16	16	12
		19					14	16	14
		17					15	14	13
		15					15		13
		15					13		13
		13							13
		13							14
									15
									13
									13
									14
	—	—	—	—	—	—	—	—	—
Average for levels under 20	17.0	14.8	16.1	15.0	16.6	12.5	16.8	13.8	14.0

Thyroid Treatment 37 Days

Interval Between Estrous Peaks During Treatment

	4	4	4	4	4
	4	4	4	3	4
	5	4	4	5	4
	5	4	4	4	4
	4	4	4	4	4
		4	4	4	4
		4	4	4	4
		4		3	4
					3

Total Length of Cycles After Treatment

	21	18	18	17	16
	20	18	19	17	14
	18	20	14		14
			14		16
	—	—	—	—	—
Average after treatment		19.7	18.7	16.3	17.0	15.0

latency period appears to be longer for the rats that showed cycles (Types I and II) than for the rats without cycles (Type III) (41.8 and 36.5 days, as compared with 27.3 days, respectively). It was shortest for the two rats treated with 200 μc. (11.5 days). That the abnormal cycles did not make their appearance for some time later, not until after an average of 69.0 and 67.0 days, respectively, for the Type I and II rats, is shown in Table 1, Column 6.

Characteristics of Abnormal Activity Cycles: Table 2 shows the total lengths of the successive cycles for the six rats with Type I cycles and the three rats with Type II and III cycles. The first few cycles of the six Type I rats were longer than 20 days, shown above the dividing space; the others were shorter, shown below the dividing space, with averages of 12.5 to 17 days. For the three Type II and III rats the total lengths averaged 16.8, 13.8, and 14.0 days, respectively.

Each cycle was divided into an inactive and an active phase. The inactive phase constituted the chief characteristic of the abnormal cycles.

Table 3 gives the lengths of the successive inactive phases for the nine rats. The lengths remained nearly constant throughout the entire observation periods for any one rat, and, furthermore, they were much the same for all nine rats. The averages ranged from 13.0 to 15.5 days—the mode was 13.

Thus, any changes in total lengths of the cycles resulted from changes in the active phase. In the rats of Type I the first few active phases were longer than the inactive phases, and after that shorter, finally leveling off at a single-day burst of activity.

The inactive phase thus becomes the most characteristic feature of the abnormal cycles.

Effect on Food Intake.—Treatment with I^{131} reduced food intake after a latency period of several weeks, just as it did activity. Abnormal activity cycles did not appear in any of the rats until food intake had reached a level well below normal (Fig. 8).

TABLE 3.—*Length of Inactive Phases of Successive Cycles, in Days*

	Type I						Type II		Frontal Lobectomy
	133BC	131BC	154BU	153BU	146BU	145BU	152BU	148BU	304BX
	13	13	12	15	13	16	12	14	12
	13	12	15	16	14	13	13	13	14
	14	12	17	15	13	13	15	12	12
	13	15	15	16	14		16	13	15
	13	17	16		12		13	12	14
	12	14	9		12		11	16	12
	Killed	13	19				14	16	14
		13	15				15	14	13
		13					15		13
		20					13		13
		13							13
		14							14
		17							15
		15							13
		15							13
		13							14
		13							
Average	13.0	14.2	14.8	15.5	13.0	14.0	13.7	13.7	13.3
					Thyroid Treatment 37 Days; Then Stock Diet				
			20	18	18		17	16	
			20	18	15		17	14	
			18	20	14			14	
					14			16	
Average			19.3	18.7	15.3		17.0	15.0	

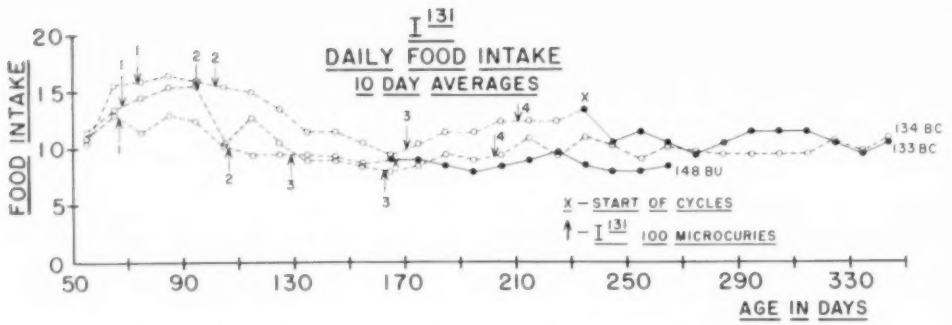

Fig. 8.—Graph showing daily food intake curves (10-day averages) for same three rats whose curves for activity are shown in Figure 2.

The rats with the best abnormal cycles in activity also showed cycles in food intake, but, with one or two exceptions, the cycles were not as clear-cut. None of the other rats showed the abnormal cycles in food intake.

Latency Period: Table 1 (Column 7) shows that for the Type I rats the average latency period of the decrease in food intake was 27.5 days; for the Type II rats, 24.0 days, and for the Type III rats, 20.6 and 18.5 days. Here, again, changes showed up first in Type III rats. In most instances food intake decreased some time before the appearance of the abnormal activity cycles (27.5 days, as compared with 69.0 days, and 24.0, as compared with 67.0, for the Type I and II rats, respectively [Columns 6 and 7]).

Characteristics of Abnormal Food-Intake Cycles: Figure 9 shows two abnormal-activity and food-intake cycles of a Type I rat (131BC). The food-intake cycles are inverted with relation to those for activity;

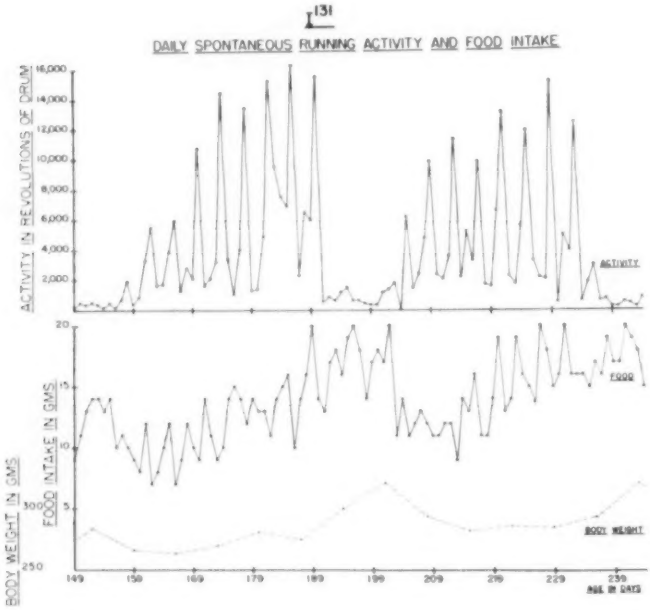

Fig. 9. — Graph illustrating inverse relationship between spontaneous activity, on the one hand, and food intake and body weight, on the other, in two abnormal cycles in a Type I I^{131}-treated rat (131BC).

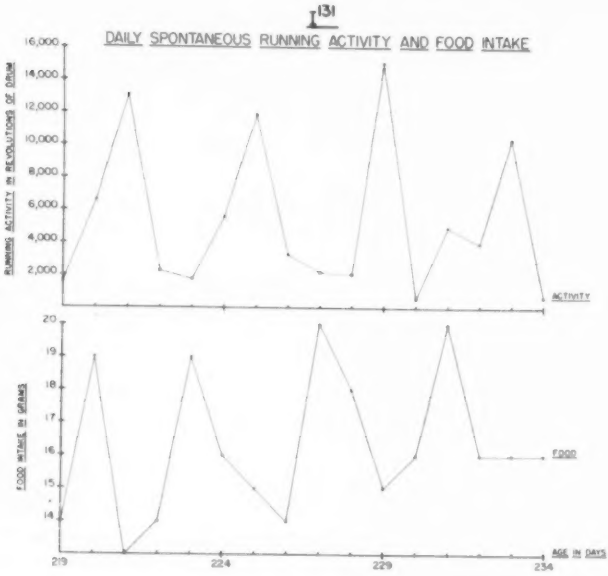

Fig. 10.—Graph illustrating inverse relationship between activity and food intake in four four-day estrous cycles in the same I^{131}-treated rat (131BC).

that is, the rats ate most when they were least active and vice versa. This same relationship was present when the four- to five-day estrous cycles appeared in food intake.

A study of the individual cycles showed that in almost every instance the first sign of the appearance of an abnormal cycle of food intake preceded by one or more days the onset of an abnormal cycle of activity.

Furthermore, in three of the rats showing the long abnormal cycles, the four- or five-day estrous peaks also were clearly present in food intake, as may be seen in Figure 10. This is of significance, since the four- to five-day estrous cycles of food intake are only very rarely present in food intake of untreated normal rats under the conditions of our laboratory, and then never so marked as in those rats with the long abnormal cycles.

Effect on Water Intake.—After the first treatment with I^{131} a small decrease in water intake was detected in almost every one of the 16 rats. In the Type I and II rats it occurred later than the decrease in food intake; in the Type III rats, earlier. After its first decrease, water intake remained quite constant and did not show either the abnormal longer type or the four- to five-day estrous cycles.

Table 1, Column 8, shows that the decrease in water intake after the last treatment did not occur until 54.4 days on the average for the Type I rats, until 39.5 days for the Type II rats, and until 18.3 and 16.0 days, respectively, for the two groups of Type III rats.

Effect on Body Weight.—Level of Body Weight: In spite of the marked decrease in food intake that occurred in all of the rats, there was little or no decrease in the rate of growth, as may be seen in the curves of body weight for the respective Type I, II, and III rats in Figure 11. Only 1 of the 16 rats actually lost a slight amount of weight; all of the others continued to grow at the normal rate for rats of our colony. This finding further substantiates the belief in the lack of any serious systemic effect of the I^{131} treatment in the doses used.

The abnormal cycles could be detected in body weight in only the rat (131BC) that showed the clearest-cut cycles of activity and food intake. Although the increases in

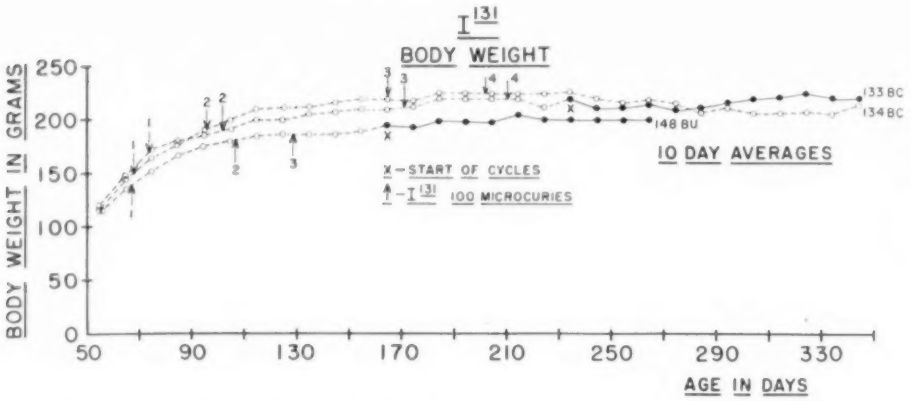

Fig. 11.—Graph showing body weight in 10-day averages for same three rats whose curves for activity were shown in Figure 2.

body weight were very small, when they did occur, they paralleled those of food intake and so were inverted with relation to activity.

Effect of Treatment with Thyroid Powder.—Five rats showing the regular abnormal cycles of Type II were treated with thyroid (thyroid powder* mixed in the stock diet in a 0.02% mixture) for 37 days.

* Supplied by Armour and Company, Chicago.

Figure 12 shows the record of one of these rats. This Type II rat (148BU) had received treatments with I^{131} at the ages of 64, 108, and 132 days. It showed the abnormal-activity cycles from an age of 158 days until shortly after the start of the thyroid treatment. Treatment was started near the middle of an inactive phase. The length of this inactive phase was shortened to 12 days; then the inactive periods were

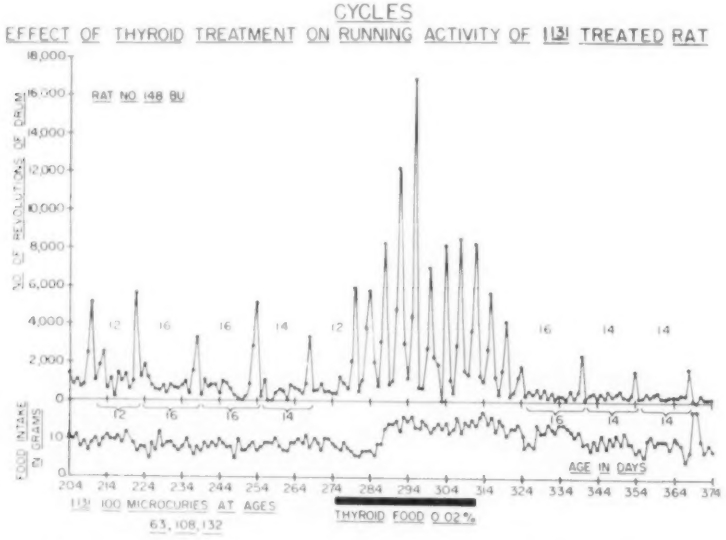

Fig. 12.—Graph showing disappearance of abnormal cycles of spontaneous running activity during 37 days' treatment with desiccated thyroid administered in food (0.02%) and their reappearance after the end of the treatment.

eliminated altogether, leaving only the normal regular succession of four-day estrous peaks. Food intake decreased during the first 11 days of treatment, then increased to almost twice its pretreatment level, at which it remained throughout the treatment period and for about 28 days thereafter. The abnormal long cycles did not reappear until 14 days after the end of the treatment. The data at the bottom of Table 2 show the length of the intervals between the estrous peaks during treatment and the total length of the long cycles after treatment. Table 3 shows that the inactive phases were slightly longer after treatment than before.

Clinical Findings.—Exophthalmos was marked in three rats with cycles and in two without cycles. Large calluses on the heels of hindfeet were found in four rats. These calluses seemed to change in size from time to time, but we were not able to determine whether the changes corresponded with abnormal activity cycles. Otherwise, all animals seemed to be in good health.

The lack of any marked or consistent external changes in the animals, such as loss of weight, loss of hair, or edema, may account for the fact that previous workers failed to detect the presence of cycles in any of their rats treated with I^{131}. Thus, in these, as in previous experiments, daily measurements of spontaneous activity made it possible to detect changes in behavior and metabolism that otherwise might have been overlooked.

Autopsy Findings.—Six of the eight rats with abnormal cycles were autopsied at a time when they were showing the cycles; five of the rats without cycles were autopsied after their activity had reached a flat low level. The other rats were used for additional observations, and so were not autopsied at all or not until long after the rat had been started on other diets or hormone treatments.

Thyroid: Some thyroid tissue was found in the rats that had shown abnormal activity cycles, but the tissue was present in only small, scarcely detectable amounts and was scarred. The follicles were sparse and very small and contained little colloid. In the rats that did not show abnormal cycles the remnants were even smaller, and in some instances no thyroid tissue could be found at all, even by inspection under a dissecting microscope.

Ovaries: There was no great difference between the ovaries of cycling and those of noncycling rats. In all instances corpora lutea made up most of the ovary. There were a few follicles and some interstitial tissue. We did not in any instance get an ovary from an animal at the height of an active phase.

Pituitary: The pituitary glands of the animals weighed more in Type III than in Type I and II rats. Histological examination revealed no abnormalities except for a deep-black pigmentation of the gland of one rat without cycles and of two rats with cycles.

Adrenals: The adrenals of the rats with abnormal cycles had normal morphology, but the cortex of one rat without cycles had a large nodule of hyperplastic cells that stained poorly with Sudan IV.

Other Glands: The other glands did not show any noteworthy changes.

Inactive Phase and Pseudopregnancy

What is the origin of the inactive phases? Before attempting to answer this question, we should keep in mind their characteristics: (1) length (13-14 days); (2) increased food intake and body weight; (3) decreased spontaneous running activity; (4) diestrous smears (no four-day estrous cycles of activity), and (5) the presence of persistent corpora lutea.

What in the rat functions at this rate and has the same characteristics? The four- or five-day estrous cycles definitely are much shorter; the gestation period of 22 days is much longer.

Pseudopregnancy, however, has much the same length and the same characteristics. This phenomenon can be elicited in various ways, but for the moment it will suffice to

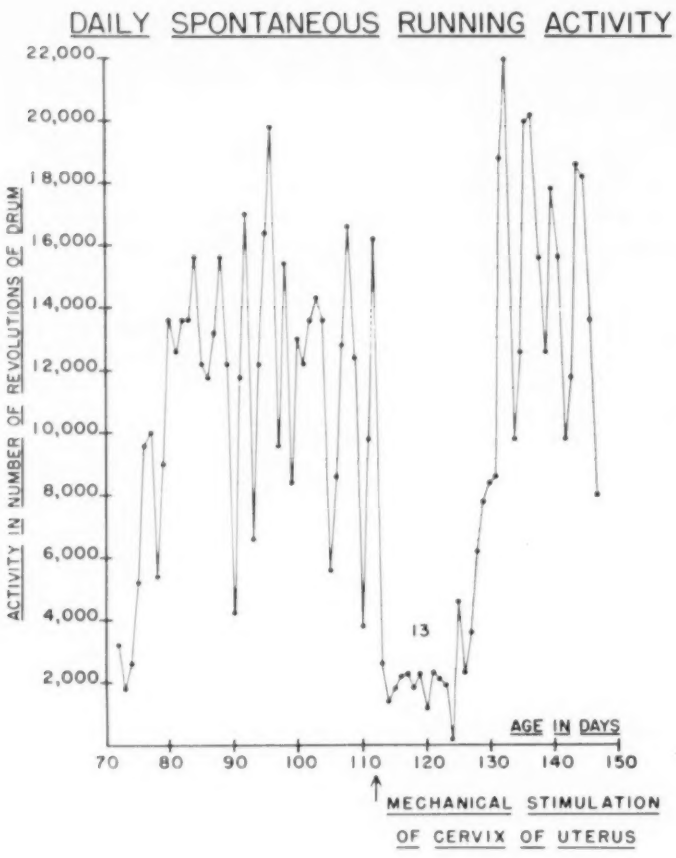

Fig. 13.—Graph showing pseudopregnancy effect on daily spontaneous activity produced by mechanical stimulation of the tip of the cervix. (data from Wang,[40] 1923).

state that it can be elicited by mechanical or electrical stimulation of the tip of the cervix or by sterile mating—if performed at the time of estrus. The rat suddenly becomes almost totally inactive, starts to eat more food, to gain weight, and to show diestrous smears with persistent corpora lutea. Figure 13 shows the effect produced by mechanical stimulation of the cervix on spontaneous running activity (Wang[40]). The cervix was stimulated early in the evening of the peak night of running activity. Activity dropped at once to a low level, at which it remained for 12 days and then increased to a small peak on the 13th day. This inactive period thus closely resembles the inactive phases of the I^{131}-treated rats. Pseudopregnancy has an average length according to Long and Evans[17] (1922) of 12-14 days, to Shelesnyak[29] (1941) of 14.03 days, and to Slonaker[32] (1929) of 14.5 days. The evidence leaves little doubt but that the inactive phase and pseudopregnancy are the same. Deciduoma formation was not attempted in the cycling rats because the possibility of a relationship between these two phenomena did not occur to us until long after the termination of the experiments. However, we have been able to produce deciduoma in rats showing cycles from other forms of thyroid deficiency.

The differences between the two phenomena are that pseudopregnancy depends on some form of stimulation, it does not appear spontaneously, and only one pseudopregnancy period follows each stimulation.

In the I^{131}-treated rats the inactive periods recur spontaneously and indefinitely. How can these spontaneously recurring inactive periods be explained? A review of our knowledge about the mechanism of pseudopregnancy should help us to understand the inactive phases. It is now generally believed that sterile copulation stimulates the pituitary to secrete luteotropin (prolactin), that this hormone acts on the ovary to produce persistent corpora lutea, that the latter then secrete progesterone, that the progesterone inhibits the secretion of the luteinizing hormone, and that the lack of the luteinizing hormone inhibits ovulation.

Further, it is believed that the stimulation of the cervix by sterile copulation acts on the pituitary through the hypothalamus, since section of the pituitary stalk prevents the appearance of pseudopregnancy (Harris,[13] 1937). The stimulus from the hypothalamus thus must act on the luteotropin-producing cells in the pituitary.

In agreement with this general formulation are the following observations: 1. Lahr and Riddle[16] (1936) found that daily injections of prolactin (30 units) brought out two long diestrous cycles of 14-16 days in length in each of two rats. The prolactin inhibited two to three estrous cycles in each instance. These workers did not continue their injections long enough or on enough animals to determine whether the long cycles would be repeated at all or with regularity.

In experiments made in this laboratory, eight rats were injected daily with prolactin,† and observations were made on vaginal smears, activity, and food and water intake. Figure 14 shows the record of one of these rats that received 1.5 mg. for 57 days and 5.0 mg. for 55 days. This treatment brought out cycles, single-day bursts of activity for the most part, of 12 to 14

† Furnished by E. R. Squibb & Sons, New Brunswick, N. J.

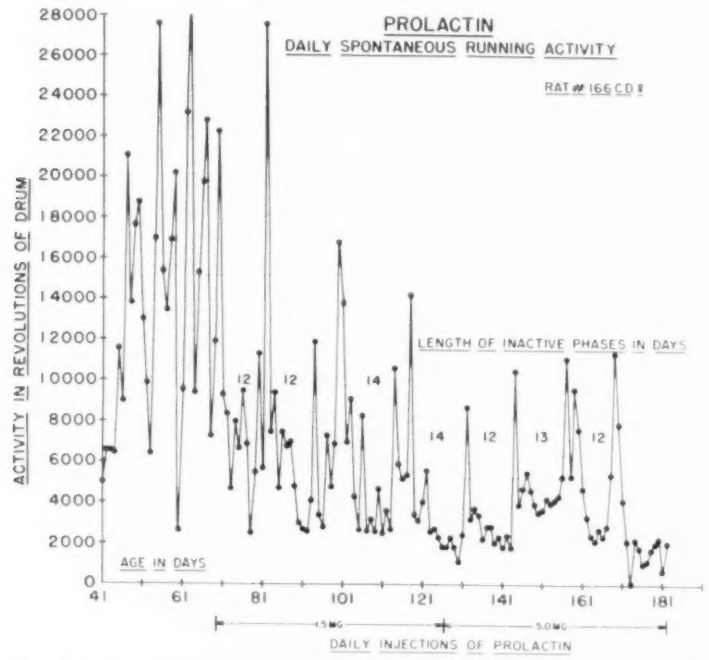

Fig. 14.—Graph showing abnormal activity cycles, 12-14 days in length, produced in a normal female rat by daily subcutaneous injections of prolactin.

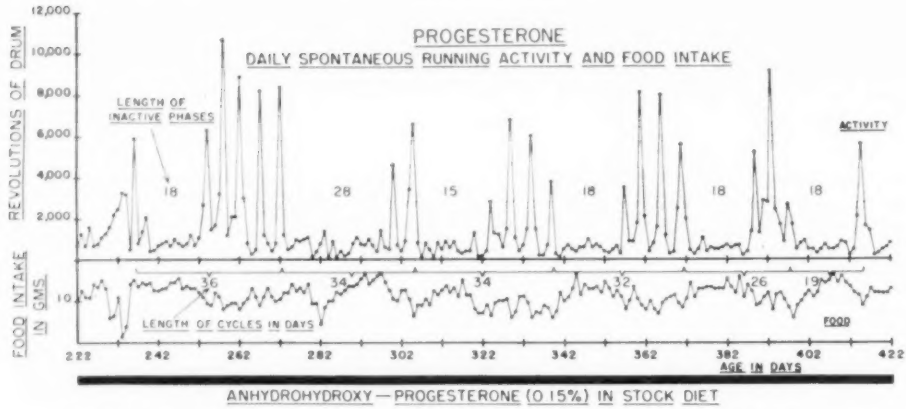

Fig. 15.—Graph showing abnormal activity cycles of a normal female rat on a diet containing 0.15% of ethisterone U. S. P. (anhydrohydroxyprogesterone).

days in length that resembled those seen in the Type II rats of the present experiments. In the prolactin-treated rats activity did not drop to as low levels in the inactive phases as it did in the I^{131}-treated rats. These experiments showed that daily injections with prolactin resulted not in continuous inhibition of estrous cycles but, rather, in recurrent temporary inhibitions.

Further experiments made in this laboratory showed that continuous treatment with ethisterone U. S. P.‡ (anhydrohydroxyprogesterone) also resulted in periodic temporary inhibition of the estrous cycle (Richter,[23] 1957). In most instances the resulting long cycles more closely resembled those of the Type I rats of the present experiment. Figure 15 shows the record of one of these rats. This rat received a diet containing 0.15% of ethisterone for 200 days. The four-day estrous cycles were interrupted, but only at intervals. Food intake showed a corresponding inverse relationship, just as was true of the food intake and activity cycles of the I^{131}-treated rats.

Thus, it is possible that the thyroxine deficiency of the rats with cycles resulted in a continuous secretion of prolactin by the pituitary, and that this continuous secretion was answered by the body by long cycles, as in Figure 13.

The part played by the great reduction in the size of the thyroid and in the amount of thyroxine produced must next be taken into account. The results of the present and the previous study showed that complete, or nearly complete, removal or destruction of the thyroid reduced spontaneous running activity to a flat low level and reduced food intake and did not produce abnormal cycles; that removal or destruction of all except a minute nodule of thyroid tissue maintained normal activity and prevented the appearance of cycles; that an amount between none at all and a small nodule that just suffices to maintain normal activity must be necessary for the production of cycles, and that thyroid treatment abolished the inactive phases and restored activity to normal.

Thus, it would appear that thyroxine deficiency removes the inhibition from the mechanism that controls the secretion of luteotropin and that thyroid treatment reestablishes the inhibition. The length of the active phases, and indirectly of the total cycles, would be a function of the rate of thyroxine secretion.

To return to the question of the permanency of the effects produced by the I^{131} treatment, the spontaneous recurrence of

‡ Furnished by Schering Corporation, Bloomfield, N. J.

the inactive phases throughout the rest of an animal's life: The possibility may be considered that the inactive phases can be elicited simply by a thyroxine deficiency. However, this would not explain why the inactive phases did not appear at once after the onset of thyroxine deficiency. The further possibility may be considered that permanent damage to the hypothalamic mechanisms upon which the prolactin release depends may be necessary for the establishment of the permanent recurrence of the inactive phases. Such damage could take place in the following way: The great reduction in the amount of thyroxine in the blood subsequent to the I^{131} treatment stimulates the homeostatic mechanisms to produce more thyroxine; the cells in the hypothalamus responsible for the thyrotropin secretion in the pituitary are stimulated; the thyrotropic cells in the pituitary increase their secretion; the thyroid responds with increased secretion of thyroxine. It is conceivable that in this process the cells in the hypothalamus or the thyrotropic cells of the pituitary become exhausted and permanently damaged. A neurological investigation of I^{131}-treated rats is now being made for signs of such permanent damage.

Finally, on the basis of these various findings, we may discuss the general biological significance of the pseudopregnancy phenomenon and the inactive phases of the abnormal cycles. To do this, it will be necessary to review the various forms of stimulation or conditions that may elicit the pseudopregnancy response.

1. Stimulation concerned directly or indirectly with the specific phenomenon of reproduction
   - Sterile copulation (Long and Evans,[37] 1922; Haterius,[12] 1933)
   - Mechanical and electrical stimulation of cervix (Long and Evans,[37] 1922; Haterius,[12] 1933; Meyer, Leonard, and Hisaw,[39] 1929; Shelesnyak,[29] 1931)
   - Nursing (Long and Evans,[37] 1922; Selye and McKeown,[31] 1933)
   - Injection of pituitary, or placental hormone (Brouha,[5] 1927; Teel,[28] 1926)
   - Injection of acetylcholine into pituitary (Taubenhaus and Soskin,[27] 1941)
2. Stimulation that produces stress and has nothing to do with reproduction
   - Trauma to intestine (Swingle et al.,[34] 1951)
   - Injection or administration of noxious substances
     - Tissue homogenates (Swingle et al.,[34] 1951)
     - Copper sulfate (intravenous) (Dury and Bradbury,[7] 1942)
     - Formalin (Selye and McKeown,[31] 1935; Swingle et al.,[33] 1951)
     - Silver nitrate to nasal membrane (Rosen and Shelesnyak,[28] 1937)
     - Chloroform (Swingle et al.,[33] 1951)
   - Injection of high amounts of drugs or hormones
     - Alloxan (Swingle et al.,[33] 1951)
     - Insulin (Swingle et al.[33])
     - Arterenol (Swingle et al.[33])
     - Epinephrine (Swingle et al.[33])
   - Forced swimming (Richter,[25] 1957)
   - Crowding of rats in same cage (van der Lee and Boot,[29] 1955)
   - Direct electrical stimulation of skull (Harris,[13] 1937)
3. Conditions of debilitation
   - Adrenalectomy (Swingle et al.,[34] 1951)
   - Starvation and vitamin deficiency (Selye and McKeown,[30] 1935)
   - Feeding of high amounts of thyroid extract Weichert and Boyd,[41] 1933)

A review of the various forms of stimulation shows that the pseudopregnancy period of inactivity or rest, associated with increased food and water intake, may serve a purpose (1) in pregnancy and lactation, to supply food and to conserve energy for the young fetuses and babies; (2) after various forms of acute severe stress, to restore energy and to permit recovery from damage done, and (3) in conditions of debilitation, to provide rest, to conserve energy to meet needs of debilitated state, and to protect the body from further debilitation.

Swingle et al.[33] concluded from their many and excellent observations that "any vigorous, non-specific stress procedure will bring about luteotropin release" in the rat. It may now be added that the pseudopregnancy response, however elicited, may serve a fairly specific purpose of restoration, rest, and conservation of energy.

In the present experiments the inactive period would serve the function of providing rest and energy for the rats debilitated by thyroxine deficiency; the greater the

deficiency the more frequent the recurrence of the periods of rest or recuperation.

Attention must be drawn to the fact that recurrent periods of pseudopregnancy are produced, on the one hand, by thyroidectomy—that is, a hypothyroid condition—and, on the other (Weichert and Boyd,[41] 1933), by a hyperthyroid condition. The feeding of high amounts of thyroid extract is the only other method of producing recurrent periods of pseudopregnancy—and then the periods are not as regular as those produced by thyroidectomy. In both instances the rats become debilitated and in need of rest or recuperation. In addition, it may be pointed out that Hollweg and Junkmann,[15] 1933, and Evans and Simpson,[8] 1930, showed that when given in small amounts, thyroxine stimulates the pituitary to secrete gonadotropin, but when given in larger amounts it inhibits gonadotropin secretion. According to the present results, large amounts must stimulate the pituitary to produce prolactin rather than gonadotropin.

Clock Mechanism

The length of the inactive phase, 12-14 days, the constancy of this length in any one rat, and the small variations from rat to rat remain to be discussed. At the present we have no definite explanation to offer, but the following considerations may be taken into account:

1. This length may represent a multiple of the estrous cycle which is found to be 4.4 days (Blandau et al.,[3] 1941); likewise, gestation may represent a multiple of the estrous cycle (Long and Evans,[17] reported an average of 21.8 days for the length of gestation; Asdell,[2] 22 days).

Multiple	of Days	
1	4.4	
2	8.8	
3	13.2	pseudopregnancy
4	17.6	
5	22.0	gestation

2. The length of life of the corpus luteum may determine the length of this phase. According to Asdell[2] (1946), the length of life and growth of the corpus luteum is about 10-14 days in most species of mammals. 3. The life cycle of the cells of the thyroid gland (Uhlenhuth,[38] 1923) may determine the length of the cycles since Williams[42] (1937) found that in rabbits the thyroid follicles undergo definite cycles—some as long as 21 days—and that they function quite independently of one another. The reduction of the thyroid to a few follicles may make it possible for them to function as a unit, and so to bring out their inherent rhythm. 4. A mechanism located in the hypothalamus, and with cycles of 14 days, may determine this length.

Comment

The results of this study showed that abnormal cycles of behavior and metabolism can be produced by radiothyroidectomy, as well as by partial surgical thyroidectomy. The cycles in the radiothyroidectomized rats were clearer-cut, more regular, and occurred in a higher proportion of rats than after surgical thyroidectomy. Owing to the clear definition of the cycle, it was possible to establish the fact that the inactive phase is the essential part of each cycle, and, furthermore, that it may play an important part in the adjustment of the rat not only to the reproductive function but to other, more general functions as well.

It was possible to produce the cycles in only 50% of the rats. Why they could not be produced in all rats is not clear. Genetic differences may play a part. It is more likely, however, that treatment with larger or smaller amounts of I^{131} may have brought out cycles in a higher proportion of rats; furthermore, the time of the treatment with relation to the estrous cycles may be a factor.

Finally, it may now be asked what light the results of this study on experimental production of abnormal cycles in rats might throw on the mechanisms underlying any of the abnormal cycles in behavior, mood, or metabolism that have been observed in human beings. In brief, how closely do the

abnormal cycles of spontaneous activity, food intake, etc., of I^{131}-treated rats reproduce any of the various types of abnormal cycles seen in mentally or physically ill patients?

Before attempting a comparison of these two phenomena, it must be kept in mind, on the one hand, that partial destruction of the thyroid by I^{131} is only one of several methods of producing abnormal cycles in rats, that each method produces specific characteristic cycles; and, on the other hand, that there are many different types of abnormal cycles in man, that the cycles are not by any means the same in all patients.

A comparison of the abnormal cycles produced by I^{131} in rats with the abnormal cycles seen in various patients showed the closest agreement with those seen in a relatively small group of catatonic schizophrenics. It is fortunate that, through the studies of Gjessing[11] (1938) and other workers (Stokes,[35] 1939; Mall,[18] 1952; Gornall et al., 1953; Danziger and Kindwall,[6] 1954), detailed daily records are at hand of many different functions of catatonic schizophrenics throughout many cycles.

The comparisons were made between cycles of spontaneous activity and food intake of the rats and cycles of mood, spontaneous activity in bed, and nitrogen balance of patients.

In length the abnormal cycles of the rats and patients are much the same, ranging from 18 to 45 days. The chief difference is that it is not known whether in patients, as in rats, the lengths may become shorter with time, finally leveling off at 18 to 20 days. So far none of the patients has been observed under controlled conditions long enough to permit the presence of such a change to be observed.

Furthermore, in both instances each cycle consists of two phases separated by sharp transition zones.

It is of special significance for this comparison that treatment with thyroid extract abolishes the abnormal cycles in the patients, just as it does in the rats. Thus, the patients, as well as the rats, may suffer from a thyroxine deficiency.

It remains to determine whether the cycles of rats show similar changes during the different phases of the cycles in pulse rate, body temperature, leukocyte count, etc., to those found in the patients. These comparisons will have to wait for the results of further observations on the cycles of rats. With these additional data, it should be possible, for instance, to determine whether the cycles of the rat can be divided into two phases of sympathetic and parasympathetic hyperactivity, as Gjessing believes is possible in catatonic schizophrenics, the abnormal phases, characterized by excitement or stupor, being associated with sympathetic hyperactivity, the intervening phases with parasympathetic hyperactivity. It will be of interest to learn whether one of the two phases of the cycle of patients represents a recuperative, protective period, as the inactive phase apparently does in rats.

Attention may be drawn here to the finding that 13-14 days is the commonest or next commonest length of cycles seen in patients with various manifestations of periodic physical illnesses (Richter,[24] 1958). Whether this is just a coincidence or an indication of the existence of a closer relationship is not known.

It is noteworthy that, in spite of the great differences in the length of the life span between rats and man and between the lengths of the ovulation periods, the abnormal cycles that depend on a thyroid deficiency have much the same length.

Summary and Conclusions

Abnormal and regular cycles of spontaneous running activity, food intake and body weight, and reproductive tract were produced in female rats by partial destruction of the thyroid gland by I^{131}.

Fourteen rats were given 100μc. by stomach tube at least once, but in most instances two, three, or four times at intervals of several months; two rats were given only

one treatment, of 200μc. The following observations were made:

1. Of 16 rats, 8 showed abnormal but regular cycles. The cycles manifested themselves in running activity and vaginal smears in all instances, but in food intake and body weight in only a few cases.

2. The existence of an abnormal cycle was determined by the presence of inactive phases, lasting 13-14 days. During this phase the rats ate more, gained weight, and showed diestrous smears and persistent corpora lutea.

3. This inactive phase of the cycle had the same length throughout all cycles in any one rat and was the same in all eight rats.

4. The active phases, the intervals between the inactive phases, were longer at the start, as long as 77 days in one instance, and then became shorter with time, usually ending at a length of only one day.

5. Frontal lobectomy brought out regular abnormal cycles in one I^{131}-treated rat that previously had not shown abnormal cycles.

6. The cycles did not usually appear for at least 40 days or more, in one instance not for 152 days after the first treatment with I^{131}, and long after food intake and spontaneous activity had decreased to lower levels.

7. At autopsy only small nodules of active thyroid tissue were found in any of the rats with cycles.

8. Thyroid administration abolished the abnormal cycles; the cycles returned after the cessation of the replacement treatment.

It is concluded that the long abnormal cycles depend on the same mechanism as that needed to produce pseudopregnancy, the only difference being that pseudopregnancy has to be elicited by some external form of stimulation, and then it occurs only once, whereas the inactive phases recurred spontaneously without any external stimulus throughout the rest of the life of the animal.

It is further concluded that the permanent appearance of the long cycles depends on damage done to nuclei of the hypothalamus as a result of the efforts of the organism to force the small remnant of thyroid tissue to secrete enough thyroxine to maintain homeostasis.

It is also concluded that the inactive phase of the abnormal cycles is a part of a mechanism that automatically provides rest or restoration for an organism, debilitated by various forms of stress or deficiencies—in the present instance, by a thyroxine deficiency.

It is pointed out that the abnormal cycles of activity or metabolism closely resemble some of the cycles seen in catatonic schizophrenics, since they have the same length and other characteristics and since both respond to thyroid replacement therapy, and also that they resemble some of the cycles of patients with periodic illness.

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REFERENCES

1. Asling, C. W.; Durbin, P. W.; Parrott, M. W.; Johnston, M. E., and Hamilton, J. G.: Evidence for Function of Aberrant Thyroid Tissue in Thymus of Rats, Proc. Soc. Exper. Biol. & Med. 94:200-201, 1957.

2. Asdell, S. A.: Patterns of Mammalian Reproduction, Ithaca, N. Y., Comstock Pub. Co., Inc., 1946.

3. Blandau, R. J.; Boling, J. L., and Young, W. C.: The Length of Heat in the Albino Rat as Determined by the Copulatory Response, Anat. Rec. 79:453-463, 1941.

4. Brobeck, J. R.; Wheatland, M., and Strominger, J. L.: Variations in Regulation of Energy Exchange Associated with Estrus, Diestrus and Pseudopregnancy in Rats, Endocrinology 40:65-72, 1947.

5. Brouha, L.: Production of Placentomata in Rats Injected with Anterior Hypophyseal Fluid, Proc. Soc. Exper. Biol. & Med. 25:488-489, 1928.

6. Danziger, L., and Kindwall, J. A.: Thyroid Therapy in Some Mental Disorders, Dis. Nerv. System 14:3-13, 1953.

7. Dury, A., and Bradbury, J. T.: Copper-Induced Pseudopregnancy in Adult Estrous Rats, Am. J. Physiol. 135:587-590, 1942.

8. Evans, H. M., and Simpson, M. E.: Some Effects on the Hypophysis of Hyper- and Hypothyroidism, Anat. Rec. 45:215, 1930.

9. Goldberg, R. C.; Chaikoff, I. L.; Lindsay, S., and Feller, D. D.: Histopathological Changes Induced in the Normal Thyroid and Other Tissues of the Rat by Internal Radiation with Various Doses of Radioactive Iodine, Endocrinology 46: 72-90, 1950.

10. Gornall, A. G.; Eglitis, B.; Miller, A.; Stokes, A. B., and Dewan, J. G.: Long-Term Clinical and Metabolic Observations in Periodic Catatonia, Am. J. Psychiat. 109:584-594, 1953.

11. Gjessing, R.: Disturbances of Somatic Functions in Catatonia with a Periodic Course, and Their Compensation, J. Ment. Sc. 84:608-621, 1938.

12. Haterius, H. O.: Partial Sympathectomy and Induction of Pseudopregnancy, Am. J. Physiol. 103:97-103, 1933.

13. Harris, G. W.: The Induction of Pseudo-Pregnancy in the Rat by Electrical Stimulation Through the Head, J. Physiol. 88:361-367, 1936.

14. Harris, G. W.: Neural Control of the Pituitary Gland, London, Edward Arnold (Publisher), Ltd., 1955.

15. Hohlweg, W., and Junkmann, K.: Über die Beziehungen zwischen Hypophysenvorderlappen und Schilddrüse, Arch. ges. Physiol. 232:148-158, 1933.

16. Lahr, E. L., and Riddle, O.: Temporary Suppression of Estrous Cycles in the Rat by Prolactin, Proc. Soc. Exper. Biol. & Med. 34:880-883, 1936.

17. Long, J. A., and Evans, H. M.: The Oestrous Cycle of the Rat and Its Associated Phenomena, Berkeley, Calif., University of California Press, 1922.

18. Mall, G.: Beitrag zur Gjessingschen Thyroxinbehandlung der periodischen Katatonie, Arch. Psychiat. 187:381-403, 1952.

19. Meyer, R. K.; Leonard, S. L., and Hisaw, F. L.: Effect of Anesthesia on Artificial Production of Pseudopregnancy in the Rat, Proc. Soc. Exper. Biol. & Med. 27:340-342, 1929.

20. Richter, C. P.: The Role Played by the Thyroid Gland in the Production of Gross Body Activity, Endocrinology 17:73-87, 1933.

21. Richter, C. P.: Cyclical Phenomena Produced in Rats by Section of the Pituitary Stalk and Their Possible Relation to Pseudo-Pregnancy, Am. J. Physiol. 106:80-90, 1933.

22. Richter, C. P.: Behavior and Metabolic Cycles in Animals and Man, in Experimental Psychopathology, edited by P. H. Hoch and J. Zubin, Grune and Stratton, New York, 1955.

23. Richter, C. P.: Hormones and Rhythms in Man and Animals, Recent Progr. Hormone Res. 13:105-159, 1957.

24. Richter, C. P.: Lengths of Cycles of Patients with Periodic Disease, to be published.

25. Richter, C. P., and Hawkes, C. D.: Increased Spontaneous Activity and Food Intake Produced in Rats by Removal of the Frontal Poles of the Brain, J. Neurol. & Psychiat. 2:231-242, 1939.

26. Richter, C. P., and Rice, K. K.: Effect of Thiamine Hydrochloride on the Energy Value of Dextrose Studied in Rats by the Single Food Choice Method, Am. J. Physiol. 137:573-581, 1942.

27. Richter, C. P., and Wang, G. H.: New Apparatus for Measuring the Spontaneous Motility of Animals, J. Lab. & Clin. Med. 12:289-292, 1926.

28. Rosen, S., and Shelesnyak, M. C.: Induction of Pseudopregnancy in Rat by Silver Nitrate on Nasal Mucosa, Proc. Soc. Exper. Biol. & Med. 36:832-834, 1937.

29. Shelesnyak, M. C.: The Induction of Pseudopregnancy in Rat by Means of Electrical Stimulation, Anat. Rec. 49:179-183, 1931.

30. Selye, H., and McKeown, T.: Production of Pseudo-Pregnancy by Mechanical Stimulation of the Nipples, Proc. Soc. Exper. Biol. & Med. 31:683-687, 1933.

31. Selye, H., and McKeown, T.: Studies on the Physiology of the Maternal Placenta in the Rat, Proc. Roy. Soc. London 119:1-31, B, 1935.

32. Slonaker, J. R.: Pseudopregnancy in the Albino Rat, Am. J. Physiol. 89:400-416, 1929.

33. Swingle, W. W.; Fedor, E. J.; Barlow, G., Jr.; Collins, E. J., and Perlmutt, J.: Induction of Pseudopregnancy in Rat Following Adrenal Removal, Am. J. Physiol. 167:593-598, 1951.

34. Swingle, W. W.; Seay, P.; Perlmutt, J.; Collins, E. J.; Barlow, G., Jr., and Fedor, E. J.: An Experimental Study of Pseudopregnancy in Rat, Am. J. Physiol. 167:586-592, 1951.

35. Stokes, A. B.: Critical Review: Somatic Research in Periodic Catatonia, J. Neurol. & Psychiat. 2:243-258, 1939.

36. Teel, H. M.: Effects of Injecting Anterior Hypophysial Fluid on the Course of Gestation in the Rat, Am. J. Physiol. 79:170-183, 1926.

37. Taubenhaus, M., and Soskin, S.: Release of Luteinizing Hormone from the Anterior Hypophysis by an Acetylcholine-like Substance from the Hypothalamic Region, Endocrinology 29:958-964, 1941.

38. Uhlenhuth, E.: The Elaboration and Release of the Colloid of the Thyroid, Proc. Soc. Exper. Biol. & Med. 20:494-496, 1923.

39. van der Lee, S., and Boot, L. M.: Spontaneous Pseudopregnancy in Mice, Acta physiol. et pharmacol. neerl. 4:442, 1955.

40. Wang, G. H.: The Relation Between "Spontaneous" Activity and Oestrous Cycle in the White Rat, Comparative Psychology Monographs, Vol. 2, Series No. 6, Baltimore, Williams & Wilkins Company, 1923.

41. Weichert, C. K., and Boyd, R. W.: Induction of Typical Pseudopregnancy in the Albino Rat by Means of Experimental Hyperthyroidism, Anat. Rec. 58:55-69, 1933.

42. Williams, R. G.: Microscopic Studies of Living Thyroid Follicles Implanted in Transparent Chambers Installed in the Rabbit's Ear, Am. J. Anat. 62:1-29, 1937.

Studies with a New Hallucinogen

Some Dosage-Response Data for JB 318

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Introduction

Previous reports indicated the structure and briefly described the effects of a new group of hallucinogens.[1,2] Sufficient experience with one of these, N-ethyl-3-piperidyl benzilate hydrochloride (JB 318), has accumulated such that dosage-response data may be presented. The present communication aims to describe more fully the effects of this agent in humans and to illuminate the relationship between its somatic and its psychologic actions.

Methods

A total of 42 observations were carried out on 39 subjects, 15 of whom were from a heterogeneous nonvolunteer group of clinic or convalescing hospital patients, and the remaining 24 were volunteer medical or divinity students or nurses, or laboratory or other hospital personnel. None was psychotic or exhibited major neurotic symptoms. All subjects were between 21 and 43 years of age; 22 were men, and 33 Caucasian. The patients were unaware of the potential effects of the compound when it was administered, but the volunteer group knew generally that they would get either a placebo or a compound that might affect some processes of mentation. All but four of the nonpatient group were paid $50 for serving as subjects and learned of the experiments through announcements or through talking with the investigators. In about half of the observations the single-blind, and in the rest the double-blind, technique was used. Observations were made individually in the same room under relatively constant conditions of illumination and room temperature. Furnishings and equipment in the room, some of which formed the basis of illusions, were not changed during the period of study. Two observers were usually present. All doses of the compound were given by mouth in the morning, the subjects being in the postabsorptive state. A number of assessments were made before drug administration and at half-hour intervals for a period of 7 to 14 hours (until the observers felt it was "safe" for the subject to return home or to the ward).

Among physical signs, salivation, pupil size, presence or absence of facial flush, pupillary light reflex, gait, and speech were observed because of atropine-like effects of the drug in earlier observations. Salivation was assessed originally by asking the subject to moisten the back of his tongue, sometimes with the aid of chewing gum, and in later observations by measuring the amount of saliva produced in one minute. The size of the left pupil was estimated to the nearest half-millimeter by comparing it with blackened circles of known diameter; the pulse was counted directly at the wrist; the light reflex was examined by shining the same small flashlight into the right eye. In a few subjects, blood pressure, body temperature, and deep tendon reflexes were also assayed.

A large number of questions designed to explore "bodily" and psychotomimetic effects were asked. These questions were based on the anticipated and observed effects of the agent in earlier observations and on questionnaires used in the study of other hallucinogenic agents.[3-5] The frequency of occurrence of phenomena elicited by such questioning is indicated in "Results."

At intervals of about 30 minutes, short interviews with the subject were carried out. The interview was designed to assess feeling-state, gross behavior, orientation, presence and nature of hallucinations, association to the hallucinations, and capacity to converse and to subtract serially 7's from 100, as a test of memory and attention.

Results

The effects of the agent on some bodily and mental functions are shown in Tables 1, 2, and 3, respectively, for three dosage levels. The number of subjects taking the placebo and each dose is indicated in the same Tables. The populations are different

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for the three dose levels, largely because of the unwillingness of subjects to take the drug a second time.

Derangements occurring in peripheral autonomic functions closely resembled those produced by atropine and scopolamine. These effects have been described for atropine in the dose range of 2 to 5 mg.[5,6] and are similar to those induced by scopolamine orally in the same amounts in our own observations. As stated earlier, blood pressure, deep tendon reflexes, and bodily temperature were not routinely assessed. Blood pressure responses were quite variable in the six subjects in whom they were measured. All six received 10 mg. of the agent. In two subjects, systolic and diastolic pressures were maximal before the drug was given and gradually decreased throughout the period of observation. In two, fluctuation was marked and unpredictable in each half-hour period, and in another two subjects, blood pressure rose during the first half-hour, reached its peak at one and one-half to two hours, and gradually fell to pretest levels at six to nine hours. In no instance did the range in blood pressure exceed 22 mm. systolic and 14 mm. diastolic. In two subjects who received 5 mg. doses, there was no appreciable change in body temperature; in only one of three subjects who received 10 mg. was there any increase in oral temperature (from 36.8 to 37.4 C [98.2 to 99.3 F]), and in two subjects who received 15 mg. a rise of from 36.6 to 37.1 C (97.9 to 98.8 F) and from 36.7 to 37.4 C (98.1 to 99.3 F) occurred.

The deep tendon reflexes in the five subjects in whom they were periodically assayed showed moderate hyperactivity as compared with predrug responses. Although our assessment of the response was based on a relatively crude clinical judgment, such an alteration was considered noteworthy, since it occurred during the intervals in which subjects who took either 10 or 15 mg. of the agent reported a feeling of bodily weakness. When hand strength

TABLE 1.—*Subjects' Statements with Bodily Content with JB 318*

Effect	Dose, Mg. 5 (N=9)	10 (N=12)	15 (N=11)	Placebo (N=7)
Dry mouth	8	12	11	2
Blurred vision	7	12	11	0
Muscle weakness	6	11	11	0
Giddiness	4	11	11	1
Difficulty in talking	3	7	9	0
Nausea	1	2	4	0
Urinary symptoms	0	2	2	0
Body or parts feel heavy	2	7	8	0
Body or parts feel light	1	5	9	0
Body or parts feel unreal	3	7	8	0
Inadequate control of bodily movements	4	11	11	0
Dream-like feeling	2	6	7	2
Bifrontal headache	2	5	7	1

TABLE 2.—*"Mental" Effects of Several Doses of JB 318*

Effect	Dose, Mg. 5 (N=9)	10 (N=12)	15 (N=11)	Placebo (N=7)
Visual hallucination	1	7	7	0
Auditory hallucination	2	6	8	0
Olfactory hallucination	0	0	1	0
Tactile hallucination	0	0	2	0
No hallucination	7	4	1	7
Anxiety	8	10	10	3
Somnolence	6	9	11	3
Ideas of reference	1	2	2	0
Disorientation	0	2	3	0
Confabulation	0	0	1	0
Delusions (unsystematized)	0	2	1	0
Lessened immediate recall	3	11	11	0
Illusions	4	8	9	1
Colors look brighter	3	5	6	0
Willingness to repeat the experiment	4	3	2	6

TABLE 3.—*Accessory Physical Findings After JB 318*

Sign	Dose, Mg. 5 (N=9)	10 (N=12)	15 (N=11)	Placebo (N=7)
Decreased salivation	7	10	11	1
Facial flush	2	7	9	0
Unsteadiness of gait	3	8	11	0
Dysarthria	3	9	9	0
Loss of pupillary light reflex	0	4	7	0

TABLE 4.—*Pulse and Pupil Size Before and Two Hours After Administration of the Drug*

Dose	Placebo		Dose, Mg.					
			5		10		15	
			Pulse					
Mean	80.9	75.1	83.1	92.2	84.3	105.7	80.5	115.1
S_d	8.9	5.4	6.7	11.9	9.2	9.0	9.7	9.2
			Pupil Size * Mm.					
Mean	3.1	3.0	3.5	4.2	3.3	4.9	3.4	6.0
S_d	0.39	0.36	0.67	0.56	0.61	0.78	0.55	0.63

* Estimated to the nearest 0.5 mm.

was measured in three subjects by having them grip a measuring device during the interval in which they reported feeling weak, it was found not to be diminished as compared with predrug assessments.

No attempt was made to measure changes in hollow viscera, but complaints referable to their function were few. The alteration in pupil diameter and pulse rate were predictable (Table 4). The coefficient of correlation between dosage and per cent increase in pulse rate was 0.52 and between dosage and per cent increase in pupil size, 0.54. Both r's were significant at a level of less than 0.01. With the subsequent addition of a more precise assessment of the decreased salivation, these three measures readily served as indices of the absorption and peripheral autonomic effects of various doses and as a basis for correlating "mental" and "bodily" effects. More precise measurement of deep tendon reflex changes should also have proved informative about central nervous system effects of the drug.

The subjects' responses about bodily states generally paralleled the visibly altered bodily functions; i. e., complaints of dry mouth, blurred vision, dysarthria, and bodily incoordination were commoner with larger doses (Table 1). The more prominent such statements the greater the measured increase in pupil size, decrease in salivation, and unsteadiness in attempts to walk a straight line (Tables 3 and 4).

Statements that parts of the body felt light and floating, or heavy as lead, were common. Occasionally, one arm was reported as feeling light and the other as heavy. Subjects commented on feelings of unreality or a "dream-like" state. "I feel like my bones are melting away"; "My body is all pushed together like a telescope"; "I know I'm here, but it's just my body. My mind is kind of out of it. Maybe my mind is at home—just my body here." Subjects were almost always able to stand in Romberg's position. There was a disorder of gait, not of station, and concurrent difficulty in performing finer coordinated movements.

As indicated in Table 2, visual and auditory hallucinations occurred with approximately equal frequency. It is likely that auditory hallucinations occurred even more commonly than reported, since many of the "sounds heard" took the form of dishes breaking, people talking quietly, or food carts rattling. At first, some of the "sounds" were believed by the observers to be "real," since all occur commonly in a hospital. Careful and immediate investigation of the alleged sound in later experiments has indicated usually that no dishes had been broken, no one had talked, and no food carts had gone by.

The presence of the relatively few tactile and olfactory hallucinations was deduced from observing the patients' behavior rather than by directly recording their statements. Tactile hallucinations were assumed present in two subjects, who repeatedly brushed an area of exposed skin with the hand and

then scratched the same area. An olfactory hallucination was assumed in another subject, who held his nose and said, "Phew."

The subject matter of about 80% of the hallucinations appeared to be based on the volunteers' experience of the past two or three weeks. The remainder of the hallucinations took their origin in childhood events. The period between childhood and the recent past was in no case the source of hallucination. Each visual and auditory hallucination lasted only a few seconds, at most a minute, in the majority of instances. With doses of 10 mg., visual and auditory hallucinations were more likely to occur independently; i. e., a subject "heard" something, and then a few moments later "saw" something, unrelated to what he had "heard" previously. With the larger dose, a figure might be "seen," "heard," and engaged in conversation at the same time.

The illusions and visual hallucinations were not as a rule bizarre, but were related to everyday experiences. A research psychologist hallucinated stacks of notebooks and yellow sheets covered with data. A laboratory technician "saw" white mice tumbling out of a box. A hospital patient "saw" a row of "student nurses six inches high in blue uniforms." The commonest type of visual hallucination was an image of a roommate, a close friend, some person seen every day. Other visual hallucinations occurring much less commonly, or only once, were dimly colored, amorphous forms, clouds of smoke, plaid patterns, spots, "dancing lights," butterflies, babies, snowdrifts, ants, mice, snakes, kangaroos, monsters "with green teeth," or wearing "hoods," and attending physicians. Among the more bizarre responses, one subject reported that he was exhaling green vapor; another, that his arm came out of its socket and was "walking by itself." There was a notable lack of sexual or aggressive imagery reported.

The majority of visual hallucinations had no plot or continuity, consisting solely of a single image seen briefly. In a few cases, however, notably those involving childhood experiences, the hallucinations exhibited a plot. One subject "saw" again an event that occurred when she was 6 years old. Her 4-year-old brother fell down some steps, cut his chin, and was bleeding profusely. She recalled that this was an event she had experienced before, and she felt as though she was reliving it. The fright that she remembered feeling in childhood was also part of the present experience.

Some subjects reported that colors looked brighter than usual, and one stated that red objects fluoresced. As a rule, however, the visual images were not vividly or elaborately colored.

Illusions were predictably determined by the subjects' preoccupations immediately before the development of the false perception. A girl who was telling about a frightening childhood experience involving snakes suddenly interpreted a strip of black felt on the ceiling as a snake. A medical student, who had been reading a Civil War volume less than an hour before taking the drug, saw Abraham Lincoln on the wall, an illusion originating in two black smudges. A divinity student, who had just reread the book of Joshua, saw a large brass pipet container as a ram's horn.

Auditory effects were about equally divided in frequency among (1) human voices, (2) musical sounds, and (3) generally harsh or inharmonious effects, allegedly made by inanimate objects or mechanical contrivances. The voices were usually those of a roommate or classmate, someone seen every day. With smaller doses of the drug, only a single sentence was "heard"; with larger doses, there might be a stream of talk. The import of the statements heard exhibited no predictable pattern. A divinity student heard his roommate say: "Whatever you do, Dave, do it with hard work." A medical student heard his name called repeatedly. A nurse heard two people whispering "bad things" about her, but she could not hear exactly what they were saying. Three patients on separate occasions heard someone say: "Go away," and stated that they would, indeed, have

preferred not to have taken part in the experiment at that time because of the unpleasantness and anxiety they were experiencing. Crying babies were reported by another patient and three medical students.

Among the musical sounds, radios playing (notable absence of TV), whistling, and bands playing were commonest. The subject was usually able to identify the tune heard and would sometimes have associations to the title or the first line of the song that seemed related to past experience. One patient who "heard" the "Song of India" immediately remembered being told that the ward was going to get a new doctor who "had a Chinese name." A detailed account of such associations is beyond the scope of the present report.

Some of the nonvocal, nonmusical "sounds heard," such as dishes breaking and food carts rattling, were described. Others reported were dogs barking, radiators banging, airplanes droning overhead, wind "wailing" or "howling," and rustling noises.

Subjects commonly reported that the hallucinations, anxiety, and diminished recent recall occurred in waves; that is, they might have profound difficulty in concentrating, experience anxiety, and hallucinate for a period of two to five minutes, alternating with intervals of equal duration during which there were no hallucinations, no anxiety, and more acute recent recall. Such alterations in mentation were not related to the presence or absence of observers, although all subjects felt more comfortable when observers were present.

It will be noted (Table 2) that by no means all subjects hallucinated, even with larger doses. Occasionally, a subject would peer intently into a corner or appear to talk with someone, and then state that he had not hallucinated and deny the event. Even taking this sort of occurrence into consideration, there were still some subjects in whom hallucinogenic effects were not produced by doses up to 15 mg.

The coefficient of correlation between all pulse-rate and pupil-size measurements

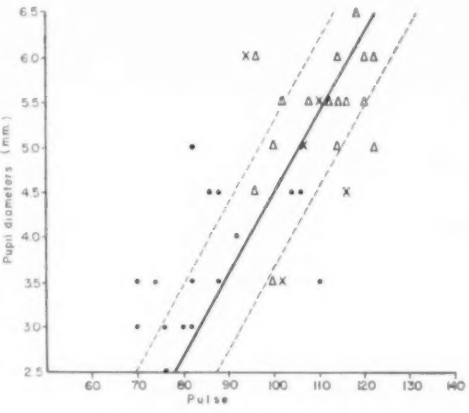

Fig. 1.—Pulse rate plotted on pupillary size.

made two hours after administration of the drug was 0.69. The regression line of pulse rate on pupil size and two standard errors are plotted in Figure 1. The black dots represent the pupil and pulse measurements for subjects who took either 10 or 15 mg. and exhibited hallucinations, and the crosses, data on those subjects who did not hallucinate after 10 or 15 mg. of the drug.

The pulse rate and pupil size of the subjects who did not hallucinate after 10 or 15 mg. doses were not grouped in any characteristic way, nor did their location on the plot indicate a difference from the distribution for those subjects who exhibited hallucinations at the same doses. Accordingly, we postulate that factors other than absorption of the drug determined the occurrence and reporting of the hallucinations.

The most predictable effect of the drug on mentation was a decrease in immediate recall. With the 10 and 15 mg. doses, such an alteration was almost invariable. Subjects usually had some difficulty in maintaining a conversation. When they reached the middle of a sentence, they sometimes could not remember what they had started to say. In all subjects, immediate recall was assayed by requesting them aloud to subtract serially 7's from 100. They either could not complete the procedure or made many errors in subtraction. This effect uniformly

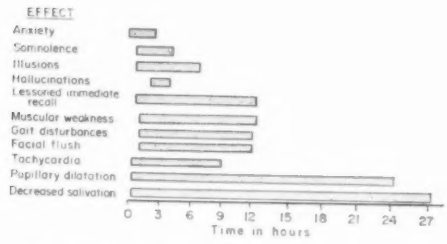

Fig. 2.—Time course of a representative experiment with 10 mg. of JB 318.

preceded and outlasted the hallucinogenic effect (Fig. 2).

Disorientation was uncommonly produced. All subjects gave proper answers to the usual questions: "Where are you?"; "What is today's date?" and "Who am I?" In a few cases, after answering these questions correctly, they would say: "Gee, this hotel has small rooms," or "Guess I'll help with the dishes." Subjects making such statements were adjudged disoriented in spite of the fact that they did not appear to be so on direct questioning.

A 20 mg. dose of JB 318 was given only to three subjects. In all three, a toxic delirium occurred which persisted for 12 to 30 hours. It is likely that the disorientation, confusion, and physical restlessness which followed the administration of these doses are predictable features of the response to larger amounts of this agent.

Delusions and ideas of reference did occur, but in less than one-third of the experiments. Among the patient group, the usual statement was that the doctor was trying to control their thinking. One medical student said to one of us: "I'm not sure of your motives in this. I'd like to stop now." Such suspicions were not long-lasting, usually having dissipated within 24 hours. One extraordinary response occurred in a divinity student, which will be reported in detail as a part of a subsequent publication. Briefly, this subject accused two observers of being homosexuals and preparing to assault him, ran into the women's dormitory to be "safe," and finally crawled into bed with his roommate in the men's dormitory.

Anxiety was common during the first two hours after administration of the drug. Later, when somnolence and decrease in immediate recall became more marked, anxiety was usually denied. It is not possible clearly to delineate the cause of the anxiety. It may be induced partly by a direct drug effect or be a response to anticipated or current psychological experiences. Certainly, some of the subjects exhibited bodily signs and verbalizations compatible with anxiety even before they swallowed the drug. Furthermore, this feeling-state occurred in almost half of those who took a placebo in the first two hours following its administration.

At doses of 10 or 15 mg., 1 of the 7 who were not paid and only 4 of the 16 who were paid for serving as subjects were willing to repeat the experiment, even for $50. As stated in earlier publications, the experience was generally described as unpleasant or frightening.

Judging by the response to placebo, some of the somnolence reported was not a pharmacologic effect of the drug. Although somnolence occurred regularly with the larger doses, none of the subjects slept. They reported that closing their eyes did not always alter the visual imagery and that enough anxiety remained to render sleep difficult.

The development of tolerance to the drug was not specifically investigated. However, observations on three subjects who took the agent for several months make it likely that tolerance to the hallucinogenic effect does occur. Three subjects received the drug in an attempt to control the tremor of hepatolenticular degeneration. In each case hallucination occurred with the first three or four doses of 10 or 15 mg. and not subsequently, although the dosage was maintained at levels of 10 or 15 mg. twice daily. With one subject the drug was discontinued for a week. When drug administration was resumed at the same dose of 10 mg. twice daily, he hallucinated again for the first two days only. No tolerance to the pupil dilatation or decreased salivation occurred.

Comment

Auditory hallucinations and the subjects' unwillingness to take the agent a second time were unique effects induced by the compound. An experimental comparison of the psychotomimetic effects of this agent with those of lysergic acid diethylamide (LSD) and scopolamine is under way. It appears currently that scopolamine, orally administered, induces greater somnolence, less anxiety, more disorientation and confusion, and fewer visual and auditory hallucinations in 5 mg. doses than N-ethyl-3-piperidyl benzilate (JB 318) evokes in 15 mg. doses.

The hallucinogenic effects of JB 318 differ in several respects from those reported as occurring after LSD. The frequency of auditory hallucinations and anxiety induced by JB 318 has already been described.

Brightly colored and elaborately formed hallucinations are commonly reported after LSD,[3,4,7,8] yet were unusual in our observations. None of the subjects who took JB 318 reported "x-ray vision," "animal paws," "melting" or partial obscuring of facial images, and gross distortion in perception of the size of an arm or a leg, effects commonly reported after LSD. On the other hand, some effects described for LSD also occurred with JB 318. These included moving or jumping of objects; bulging or rippling of flat surfaces, such as walls and ceilings; a sense of keener hearing; feelings of "lightness" or "heaviness," and depersonalization. Among bodily effects, mydriasis, hyperreflexia, and hyperthermia occurred with both agents, but the predictable blood-pressure-elevating effect of LSD was not apparent after JB 318. The decreased salivation induced by JB 318 has not been reported as an effect of LSD.

The variability of the hallucinogenic response in different subjects, both in its intensity and in its qualitative aspects, is being examined by correlating alterations in autonomic activity, prior and repeated psychological test performance, and psychotomimetic effects. We are attempting by means of pretest interviews, utilizing free-association techniques, and by psychometric procedures to predict the nature and intensity of the changes in mentation and perception.

Three subjects who took 10 mg. of the agent with relatively little psychotomimetic effect did take the drug a second time. For these subjects, only the data for the first experiment are shown. In each case, florid visual and auditory hallucinations and anxiety occurred on the second occasion. Test-retest experiments therefore call for critical examination.

About half the subjects who took the compound exhibited speech, behavior, and psychological test performance compatible with a hypomanic state, beginning about 48 hours after drug effects were dissipated and persisting for several months. The determinants, mechanisms, and dynamics of this effect are being studied.

The frequency of occurrence and intensity of the autonomic and psychotomimetic effects in the patient group did not differ significantly from those of the student-hospital employee group. There was a slight tendency to more disorientation among the former, and to greater anxiety and better verbalization of drug-induced experiences in the latter. The subject matter of the hallucinations and illusions, and the way in which all drug effects were described, did show differences, presumably based on differences in life experience, education, and degree of psychiatric sophistication.

We are using this agent to learn more about higher integrative and preceptive functions of the brain, rather than to develop analogies about the etiology of mental illness.

Summary

Dosage-response data for some effects of N-ethyl-3-piperidyl benzilate (JB 318) are described.

With doses in the range of 5 to 15 mg. given orally in humans, atropine-like peripheral autonomic effects were induced.

Following administration of the same doses, anxiety, somnolence, illusions, visual and auditory hallucinations, decreased immediate recall, and feelings of "unreality" or a "dream-like" state predictably occurred.

Tactile and olfactory hallucinations, delusions, and ideas of reference were at times noted, but were not predictable in their occurrence.

In doses of 20 mg. or greater, it is likely that a true toxic delirium is induced by this agent.

The peripheral autonomic effects and psychotomimetic effects paralleled each other in intensity.

Individual differences occurred in degree and type of hallucinations and illusions.

Experiences of the immediate past or of early childhood largely determined the subject matter of the illusions and hallucinations.

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REFERENCES

1. Ostfeld, A. M.; Abood, L. G., and Marcus, D. A.: Studies with Ceruloplasmin and a New Hallucinogen, A. M. A. Arch. Neurol. & Psychiat. 79:317-322 (March) 1958.

2. Abood, L. G.; Ostfeld, A. M., and Biel, J.: A New Group of Psychotomimetic Agents, Proc. Soc. Exper. Biol. & Med. 97:483-486 (Feb.) 1958.

3. Abramson, H. A.; Jarvik, M. E.; Kaufman, M. R.; Kornetsky, C.; Levine, A., and Wagner, M. J.: Lysergic Acid Diethylamide (LSD-25): I. Physiological and Perceptual Response, J. Psychol. 39:3-60 (Jan.) 1955.

4. Isbell, H.; Belleville, R. E.; Fraser, H. F.; Wikler, A., and Logan, C. R.: Studies on Lysergic Acid Diethylamide (LSD-25): Effects in Former Morphine Addicts and Development of Tolerance During Chronic Intoxication, A. M. A. Arch. Neurol. & Psychiat. 76:468-478 (Nov.) 1956.

5. Berger, A. R., and Ballinger, J.: The Relative Toxicity of Atropine and Novatrine in Man, Am. J. M. Sc. 214:156-158 (Aug.) 1947.

6. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, Ed. 2, New York, The Macmillan Company, 1955.

7. DeShon, H. J.; Rinkel, M., and Solomon, H. C.: Mental Changes Experimentally Produced by L. S. D. (d-Lysergic Acid Diethylamide Tartrate), Psychiat. Quart. 26:33 (Jan.) 1952.

8. Bercel, N. A.; Travis, L. E.; Olinger, L. B., and Dreikurs, E.: Model Psychoses Induced by LSD-25 in Normals, A. M. A. Arch. Neurol. & Psychiat. 75:588-618 (June) 1956.

CORRECTION

In the book review, *Reticular Formation of the Brain*, which appeared in the January issue of the ARCHIVES, the third sentence of the third paragraph should read as follows: Thus Livington looks upon the brain as functioning as a whole as a "transactional mechanism"; Jasper looks forward from a structural concept to the importance of temporal patterning and differentiated patterning in the function of the nervous system as a whole, and Walker reminds us that "although the cerebral cortex may be only a suburban area, a functional disturbance of it is devastating to the nature of the organism even if the reticular formation be intact."

Books

BOOK REVIEWS

Technic and Practice of Psychoanalysis. By Leon J. Saul, M.D. Price, $8.00. Pp. 244. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia, 1958.

The spirit and flavor of this book are exemplified in these words from the Preface: "The technic of modern psychoanalysis, with reasonable correctness, might be distilled to this quintessence—the analyst must understand and bring the patient to understand as quickly, accurately and thoroughly as possible the patient's present emotional life as it is related to and is an outgrowth of his past, particularly of the pattern shaped during his most formative years (0 to 6) by the influences on him. Then, in the individual sessions, the analyst discerns and repeatedly shows the patient, through the common element (the red thread) of the associations, especially as seen in dreams, the central, presenting motivational point of each hour and the disordered childhood emotional pattern which this is repeating in life, especially, and consistently as this pattern is transferred from the childhood figures to the analyst. The goal of so doing is to recondition the patient and correct the disordered parts of the pattern.... It should be the analyst's aim to achieve secure progress on this path with a minimal number of sessions and in the shortest period of time."

Saul's book is divided into two parts, the first about forty pages long and the second about two hundred pages. The former is entitled "Approach: What Is to Be Accomplished" and includes chapters on (1) the nature and goals of psychoanalytic treatment, (2) attitudes of the analyst, and (3) theoretical base of treatment. The theoretical section is quite short. Considerations having to do with the nature of the psychic apparatus and with psychoanalytic psychopathology are for the most part implicit rather than otherwise.

The second part of the book is entitled "Practice: How to Accomplish Therapeutic Goals." There are five sections, as follows: (1) Beginning Stage; (2) Materials; (3) Conduct of the Analysis; (4) Some Special Problems, and (5) Progress in and Termination of the Analysis. In the first section Saul stresses the importance of careful history-taking and therapeutic management of initial interviews. As is the case throughout the book, he illustrates his points with a wealth of clinical examples. He stresses the opportunity for diagnosing the nuclear dynamics in the first interview. Beyond this, it is important to utilize every available source of information about the patient's development from birth to the present time, as well as to be sensitive, from the outset, to signs and symptoms of unconscious associative material.

The second section—"Materials"—includes chapters on free association, understanding unconscious material, and dreams. The first of these, especially, is beautifully developed from the point of view of "really listening" for the central theme—the "red thread"—of each hour and then interpreting that in accordance with what will be ego syntonic at the time. Saul works with dreams in a way that is sometimes considered "old-fashioned"—that is, by systematically inviting associations to their component parts—but it is because dreams are still the royal road to the unconscious. His rules for the use of unconscious material, and dreams in particular, are summarized in fourteen points, condensed as follows: (1) Keep very close to the material; (2) look for the big, major central themes first; (3) keep to the level of consciousness and repression of the manifest dream and associations; (4) distinguish the dynamics from the content; (5) keep separate what is current, namely, the motivations (*a*) in the present life situation and (*b*) in the transference from (*c*) what is past, i. e., the sources of these motivations in the emotional patterns formed in childhood; (6) be alert to effects of current stimuli on dreams and associations from life and transference; (7) review the material for the libidinal and hostile motivations, and for fight and flight; (8) review the material for the ego motivations and the sexual motivations; (9) pay close attention to the sequence of the dream elements; (10) watch for the material connected with the greatest emotional response; (11) look for the positive progressive forces, as well as for the regressive ones; (12) look for the object relationships, and also relationships by identification and projection; (13) use symbols only with great caution and only in context, and (14) note what

the dreamer's ego accepts and acts on in the dream, for this is an important guide to what he will accept as interpretation in analysis and as behavior in life.

The author discusses "conduct of the analysis" in terms of its mechanics (use of the couch, frequency of appointments, etc.), interpretations, resistances, transference phenomena, and so on. He stresses ego analysis, as opposed to analysis of id content. He advocates flexibility geared to the dynamic situation of the individual patient. He is, however, as aware of the dangers of inflexible flexibility as he is of inflexible inflexibility. In effect, he contrasts the adaptability of the seasoned analyst to the doctrinaire of whatever "school" of analysis. The concluding sections on "special problems" and "termination" reflect this same spirit and approach.

In the opinion of this reviewer, Saul's book is primarily for psychoanalysts and students of psychoanalysis. As the author well knows, some of his points are still controversial. The student will wish to compare and contrast this book with those, among others, by Kubie and Karl Menninger. The "traumatic experiences" of childhood leading to nuclear neurotic patterns are, perhaps, too much explained in terms of "conditioning" or "how the child was reared"—i. e., the "actual" interpersonal relationships. The impacts of excessively strong impulses and the misinterpretations and phantasied perception of "reality" on the weak ego of the young child are often determining factors in the "childhood neurosis," including subsequently repressed archaic defense mechanisms. Clinical psychoanalysis is so very difficult partly because it is so frequently necessary to dissect out this multiplicity of pathogenic elements, which can be roughly grouped as those that come from the mistakes and neurotic influences of the parents an those that the child himself contributes because of phantasy and distortion of reality arising from the relative strength of his impulses and the weakness of his ego.

The reader of this book cannot escape recognition of the sincerity, conscientiousness, and dedication of its author. Scientific objectivity is blended with the spirit of the devoted physician. As regards differences of opinion among psychoanalysis, Saul is forthright in stating his own position, and yet his basic attitude is in the tradition of Hippocrates: "Life is short, and the Art long; the opportunity fleeting; experiment dangerous, and judgment difficult." At this stage of our development, can we ask for better?

DOUGLASS W. ORR, M.D.

Envy and Gratitude. By Melanie Klein. Price, $2.75. Pp. 101. Basic Books, Inc., 59 Fourth Ave., New York 3, 1957.

In this slender volume Mrs. Klein has set herself the task of exploring the earliest sources of two attitudes—envy and gratitude. Using poetic illustrations, as well as her own psychoanalytic language, she draws a clear and intricate picture of what she means by these two words. Observations taken from the analyses of four adult patients further illuminate her subject matter. Her perceptive and thoughtful discussion should enrich our understanding of emotional states and thereby contribute to our therapeutic effectiveness, even though most of us who are not at home in Kleinian psychology may find the reading a bit arduous.

One contribution of the book is the author's sensitive appreciation of the complex fusion of affects and fantasies which comprise both envy and gratitude, and her attempt to distinguish them from other affective states or attitudes. It is this complexity, in addition to her reconstructive method, which makes it difficult for this reviewer to find that the book adds to our knowledge of the early development of these affects. Mrs. Klein considers her reconstructions from adult analyses of the first few months of life to be logically analogous to Sigmund Freud's reconstructions of the later years of childhood. This analogy is a highly questionable one. In ascribing intricate emotions to the very young infant, she is, of course, extending her hypothesis that complex fantasy life and object relations exist at this age. Exhaustive discussions of this point are readily available in the literature and would apply to this most recent work as well. She includes no direct observations of infants or children.

We should be grateful for this contribution in the study of affects, perhaps especially because Mrs. Klein reminds us so tellingly of the rich texture of experience, conscious and unconscious, which can easily be distorted and oversimplified when described in the technical jargon of today.

MARJORIE HAYES, M.D.

Naven. By Gregory Bateson. Price, $6.00. Pp. 310, with 28 plates. Stanford University Press, Stanford, Calif., 1958.

This book was published first some twenty years ago. The main feature of this edition is a new epilogue in which the problems explored in the book are again examined but in a different frame of reference. In this manner, the epilogue is a bit like psychotherapy, in which data already known are reexamined and reinterpreted in the light of a more comprehensive view of the world. Because my own intersts are primarily in the area of the new epilogue, I shall comment mainly upon this aspect of the book.

The book as a whole reports upon an anthropological investigation of a New Guinea tribe characterized by an elaborate system of ceremonies (naven) carried out as an aspect of the relation between men and their sisters' sons. This ceremony appears to be a sort of ritual evaluation of significant events in the life of the nephew; generally it has a congratulatory flavor, as would a party given for a nephew in this culture, but it has an ambivalent character, since it can also be used in a satiric form as a negative evaluation of action. In the original investigation a large number of detailed data concerning the form and significance of these ceremonies in the life of the tribe were collected.

The 1936 epilogue discusses the significance of this material in terms of the theoretical developments of the time; the 1958 epilogue discusses some newer developments in possible theoretical treatments of the same material.

Bateson's main topic in this new epilogue is the present state of theory in the sciences dealing with human beings and their behavior. He points out that there has gradually been developing (almost unheralded) a synthetic field including elements from many others. This field is as yet so new and so indistinctly seen as to have no generally accepted name; in fact, the field cannot yet be said to have any generally accepted status. The prevailing emphasis in this field is upon epistemological considerations; various fields which have contributed include cybernetics and communication engineering, operational methods in physics, the important work of Whorf in linguistics, the modern redefinition of the relation of the philosopher to scientific problems, and the work of Cassirer and Langer in the field of symbolic forms.

If a reviewer may make a suggestion, it would seem that perhaps the most appropriate name which has been suggested is that of "kemnetic inquiry," proposed by Bentley (*Science* 112:775, 1950), from the root "ken," connoting knowing. Bentley's transactional treatment is very close to that suggested by Bateson, when he says that the "schismogenic unit is a two-person subsystem." In general agreement here also with Sullivan in denying primary status to the "individual" as a theoretical notion in this field, Bateson says: "Individual behavior [refers only to] events in one . . . arc of the schismogenic subsystem."

In his final remarks, Bateson points out the greatest difficulty encountered in any description pitched at a more abstract level than those previously available. The relation between a less and a more abstract view is always asymmetrical; the more abstract view includes the less as a special case, whereas the less abstract can in no way comprehend the more abstract. This aspect of the situation would seem to promise that the appropriate critical audience for this field will be slow in emerging. The problem is similar to that with which psychotherapists have long been familiar: "You can't understand psychotherapy unless you have been in therapy."

To this reviewer, it appears that Bateson has performed an important service in bringing to the attention of a wide audience the implications inherent in this new field of endeavor.

HARLEY C. SHANDS, M.D.

Adolescence and the Conflict of Generations. By Gerald H. J. Pearson, M.D. Price, $3.95. Pp. 186. W. W. Norton & Company, Inc., 55 Fifth Ave., New York 3, 1958.

In the preface to this latest of his five superbly written books, Dr. Pearson modestly informs us that he is presenting in as simple a form as possible some of the knowledge about adolescence gained from psychoanalytic research. He adds that the book was written for students of medicine, psychology, psychiatry, social work, and sociology, as well as the adolescent and his parents.

While recent years, and particularly this past one, have witnessed the appearance of an increasing number of articles and books on the subject of adolescence, Dr. Pearson's emphasis on the "conflict of generations" makes his approach unique. He offers us a newer and clearer understanding of the mutual effect of adult and teen-ager upon one another.

When the author tells us that several volumes could be written on each of the various aspects of adolescence which he discusses in his book, he is undoubtedly correct; yet one cannot help

marveling at the tremendous amount of compact and rich material which he presents, in a delightful style that makes for easy and fascinating reading. Perhaps I am naive in disagreeing with him when he expresses the fear that he may have oversimplified his text, for it is my belief that the early chapters at least are couched in technical psychoanalytic terminology that may greatly limit the actual understanding that he hopes to convey to the widely diversified groups of people for whom he says the book is intended.

In a beautiful exposition that blends theory and clinical facts, Dr. Pearson, drawing upon his long analytic experience with children and adolescents, paints a realistic picture of the problems of growth, of the erotic drives, of ideals, of object relationships, and of social adjustment, revealing to us the unconscious and conscious conflicts of both the adolescent and his parents.

It may appear that my great enthusiasm for this exciting little book has kept me from recognizing flaws or failings. In an effort to seek out something to criticize adversely, I can only suggest that Dr. Pearson may leave the reader with the impression that all of the problems of the female teen-ager stem from her lack of a penis. Here we may be viewing, however, some of the oversimplification to which the author refers in his introduction.

His chapter on the "Adjustment of the Adolescent to the Social Organization" is a classic, and the "Conclusion" which follows should become required reading. Let us hope that Dr. Pearson will continue to write more delightful books like "Adolescence and the Conflict of Generations."

EUGENE I. FALSTEIN, M.D.

Freud and Hypnosis: The Interaction of Psychodynamics and Hypnosis. By. M. V. Kline. Price, $4.00. Pp. 207. The Julian Press, 80 E. 11th St., New York 3, 1958.

This volume is by a psychologist who is one of the most prolific writers on the current hypnotic scene.

It is divided into three parts. The first, which is really the only one to which the title refers, is essentially a polemic. It inveighs against psychoanalysts and psychoanalysis for allegedly deriding hypnosis as a phenomenon and obstructing its investigation. It chides analysts for basing their attitudes toward hypnosis on what Freud had to say about it in a much earlier stage of its development, and bids them emulate him and admit that it is an enigma which they fear to approach. It turns the analyst's weapons back on him by arguing that analysts fear and will not work with hypnosis because the hypnotic subject can unconsciously perceive the analyst's anxieties, failings, etc., and because they shrink from dealing with the explosive interpersonal relationships engendered in the hypnotic situation. Since the reviewer is himself a psychoanalyst who has worked a good deal with hypnosis without finding himself "outside the pale"—the fate which Dr. Kline believes likely to befall those who occupy themselves seriously with hypnosis—he will leave it to others to judge the charges. To sample the flavor of the author's attitudes: "To a great extent the figure of Sigmund Freud and some of his observations have been built into a legend of hypnotic omnipotence and, on the basis of his observations and conclusions, hypnosis has been dismissed as an obstructionist element in psychodynamics to be excluded from serious consideration, let alone serious research and clinical application. In this lies one of the greatest distortions of scientific truth in modern times." (page 44)

The second section is a somewhat miscellaneous grouping of both empirical investigations and theoretical studies by the author, dealing with (1) hypnotic regression and progression (time-age orientation to the future), in which the author proposes that the hypnotic state is really a "retrogression," by which he refers to some "basic neuropsychological state"; (2) hypnotically induced deafness studied by delayed auditory feedback, in which he shows that, although the disturbance with the feedback (the subject heard his words one-fourth second after they were spoken) was much less than in the nonhypnotic state, there was still enough disturbance to distinguish hypnotic and true deafness; (3) the relief of a case of psoriasis by a method involving sensory images of changes in the skin; and (4) an investigation of temperature change under hypnosis in which direct suggestions failed, whereas the suggestion to hallucinate being in an airplane at 10,000 ft. resulted in a drop of 3 degrees (F) in five minutes or less. (It should be noted that these several experiments were each with only one subject, not the same one, although the observations were repeated.)

The third section of the book, entitled "Clinical Considerations," presents (1) a method of induction in which the subject visualizes an image of himself being hypnotized; (2) a study

of the responses to Card 12 M of the TAT (which to many people looks like a hypnotic scene) by college students and amputees, demonstrating the greater resistance of the amputees to hypnosis (confirmed by hypnotizability studies); (3) several clinical instances showing the dependence of hypnotizability on unconscious emotional attitudes; and (4) an interesting speculation, based on an experiment, that a hypnotist cannot induce antisocial behavior unless he himself can emotionally accept such behavior.

Despite this apparent diversity of parts, there is a unifying theme in the book—Dr. Kline's view of the nature of hypnosis. I shall attempt to state that view here, but I must admit that the author's rambling and turgid style, as well as his penchant for idiosyncratic word coinages without adequate definition, may have resulted in some misunderstandings on my part.

The author makes a sharp cleavage between the hypnotic relationship and the hypnotic state. This is a basic and important distinction, to which the reviewer subscribes. This hypnotic relationship the author describes in the usual terms of a transference relationship, but he departs from the usual view by insisting that this relationship need not include submissiveness or dependency on the part of the subject. While it is true that evidences of negativism are plentiful in the hypnotic relationship and true that the idea of the hypnotic subject as a submissive automaton is superficial and oversimplified, the reviewer holds it still a likely hypothesis that an important and universally present aspect of the hypnotic relation is the subject's submission.

With regard to his view of the hypnotic state, the author is harder to follow. One can readily agree with his proposal that the hypnotic state signifies many different things to different people—sleep, death, anesthesia, or sexual relationships of various kinds, for example. One can also agree that the hypnotic state serves to make possible various kinds of alterations both in interpersonal interaction and in intrapsychic functioning; but the author appears to regard the state as something different from and basic to all these, and yet not encompassed by the "parameters" of scientific thinking—whether organic or psychological—so far defined. "To attempt to restrict them [the boundaries of hypnotic phenomena] within the framework of physical science or of psychoanalytic psychology is to limit our perspective and leave us with an unresolved problem which, as for Freud, will remain enigmatic." (p. 68) The hypnotic state is conceived of variously as a complex state "which requires a broader conceptualization of the nature of human behavior—in one respect more organic in nature, in another even more dynamic than psychoanalysis"—(p. xi); as a state somehow basically linked with conditioning—"one wonders whether the very process of conditioning . . . does not obviously involve hypnotic stimulation"—(p. 76); "as a creative experience in the same sense that a dream is a creative experience" (p. 182), and as "in essence a recapitulation of the nuclear core of learning from a phylogenetic and ontogenetic frame of reference" (p. 182).

The author emerges not merely as an investigator of hypnosis but as its champion, too.

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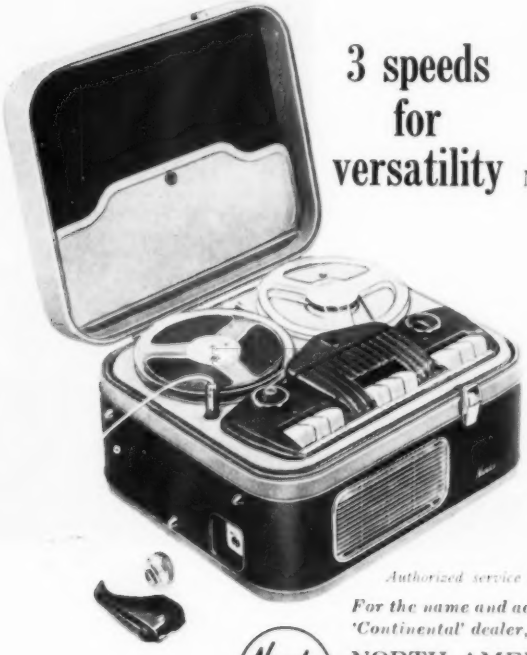

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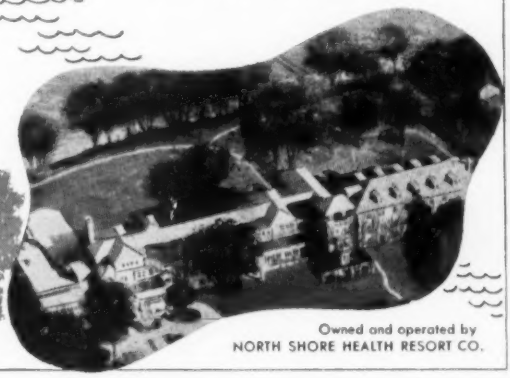

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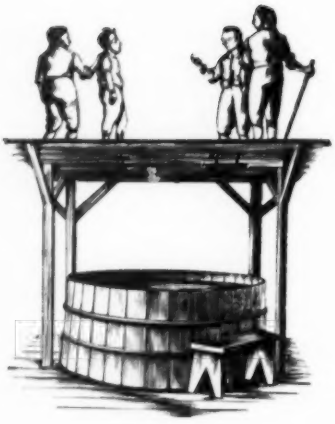

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1. Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. 2. Current personal communications; in the files of Wallace Laboratories.

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1. **Brody, J. I.** and **Bellet, S.:** Am.J.M.Sc. **233**:40 (Jan.) 1957.
2. **Impastato, D. J.** and **Gabriel, A. R.:** Dis.Nerv.System **18**:334 (Jan.) 1957.
3. **Impastato, D. J.** and **Berg, S.:** Am.J.Psychiat. **112**:893 (May) 1956.
4. **Buckley, R. W.** and **Richards, W. L.:** Ohio State M.J. **52**:481 (May) 1956.
5. **Lewis, W. H., Jr.:** Dis.Nerv.System **17**:81 (Mar.) 1956.
6. **Moore, D. C.** and **Bridenbaugh, L. D., Jr.:** Anesthesiology **17**:212 (Jan.) 1956.
7. **Jacoby, J.,** *et al.:* J.Clin.& Exper.Psychopathol. **16**:265 (Dec.) 1955.
8. **Newbury, C. L.** and **Etter, L. E.:** A.M.A.Arch.Neurol.& Psychiat. **74**:472 (Nov.) 1955.
9. **Newbury, C. L.** and **Etter, L. E.:** *Ibid.* **74**:479 (Nov.) 1955.
10. **Impastato, D. J.:** J.M.Soc.New Jersey **52**:528 (Oct.) 1955.
11. **Lincoln, J. R.** and **Broggi, F. S.:** New England J.Med. **253**:546 (Sept.) 1955.
12. **Tucker, W. I., Fleming, R.,** and **Raeder, O.:** *Ibid.* **253**:451 (Sept.) 1955.
13. **Rietman, H. J.** and **Delgado, E.:** Dis.Nerv.System **16**:237 (Aug.) 1955.
14. **Lewis, W. H., Richardson, D. J.,** and **Gahagan, L. H.:** New England J.Med. **252**:1016 (June) 1955.
15. **Glover, B. H.** and **Roisum, B. H.:** J.Nerv.& Ment.Dis. **120**:358 (Nov.-Dec.) 1954.
16. **Saltzman, C., Konikov, W.,** and **Relyea, R. P.:** Dis.Nerv.System **16**:153 (May) 1955.
17. **Robie, T. R.:** J.M.Soc.New Jersey **52**:82 (Feb.) 1955.
18. **Schiele, B. C.** and **Margolis, P. M.:** Minnesota Med. **38**:1 (Jan.) 1955.
19. **Wilson, W. P.,** *et al.:* A.M.A.Arch.Neurol.& Psychiat. **72**:550 (Nov.) 1954.
20. **Steven, R. J. M.,** *et al.:* Anesthesiology **15**:623 (Nov.) 1954.
21. **Holt, W. L., Jr.:** New York State J.Med. **54**:1918 (July) 1954.
22. **Holmberg, G.,** *et al.:* A.M.A.Arch.Neurol.& Psychiat. **72**:73 (July) 1954.
23. **Dewald, P. A., Margolis, N. M.,** and **Weiner, H.:** J.A.M.A. **154**:981 (Mar.) 1954.
24. **Wilson, W. P.** and **Nowill, W. K.:** A.M.A.Arch.Neurol.& Psychiat. **71**:122 (Jan.) 1954.
25. **Moss, B. F., Jr., Thigpen, C. H.,** and **Robinson, W. P.:** Am.J.Psychiat. **109**:895 (June) 1953.
26. **Holt, W. L., Jr.,** *et al.:* Confinia neurol. **13**:313, 1953.
27. **Murray, N.:** Texas Rep.Biol.& Med. **11**:593, 1953.
28. **Murray, N.:** Confinia neurol. **13**:320, 1953.
29. **Alexander, L., Gilbert, I. E.,** and **White, S. E.:** *Ibid.* **13**:325, 1953.
30. **McDowell, D. H., Rahill, M. A.,** and **Tyndall, J. A.:** J.Irish M.A. **31**:210, 1952.
31. **Holmberg, G.** and **Thesleff, S.:** Am.J.Psychiat. **108**:842, 1952.
32. **Altschule, M. D.** and **Tillotson, K. J.:** New England J.Med. **238**:113 (Jan.) 1948.

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